HarvardMedicine

SUMMER 2013

How Bugs Are Built

Revealing what makes pathogens tick propels the fight against infectious disease

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Special Report: How Bugs Are Built

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From the Dean

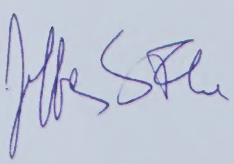
THOUGHTS ON INNOVATION

PESTILENCE CAN PROVIDE the basis for mesmerizing fiction and mortifying nonfiction. Records written on stone and in bone tell of epidemics of syphilis, smallpox, measles, and plague that have felled pharaohs, toppled empires, and decimated armies—or the peoples they conquered. Standing ready in every instance have been the medical practitioners of the time, bringing their charms, spells, masks, cups, and leeches to the fight.

Today, our approaches to identifying and controlling the causes of infectious diseases are decidedly less theatric, but they are no less intent. In this issue of *Harvard Medicine*, we look at some of the ways researchers and physicians are collaborating to cast a surveillance net wide enough to capture the movements of organisms that surface across an ocean or across the street. We also explore the meticulous work of researchers who throughout the decades have sought out molecular-level weaknesses of the microorganisms that cause some of the globe's most devastating diseases: AIDS, malaria, cholera, and tuberculosis. By contrast, we examine the legions of "good" bugs that share space with us, those microorganisms that draw out nutrients from what we eat, guide our immune responses, and generally regulate the metabolic processes that keep us healthy and functioning.

We not only investigate the forces that can perturb or protect our personal health, in this issue we also take a reflective look at the events of one tragic day in April. Our students' and alumni's recollections of the bombings in Boston serve to remind us of our vulnerability, and also of our strength. In the aftermath, the work of those at Boston Children's Hospital, Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Massachusetts Eye and Ear, Massachusetts General Hospital, McLean Hospital, and Spaulding Rehabilitation Hospital gave new meaning to community. They brought heartfelt determination and superlative skills to what became Boston Strong.

We also would like to share with you another story of community, one involving this magazine. In June, we were thrilled to learn that *Harvard Medicine* earned the prestigious 2013 Robert Sibley Magazine of the Year award from CASE, the Council for Advancement and Support of Education. We hope that you, the community served by *Harvard Medicine*, will join us in taking a moment to celebrate this achievement.



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JOHN SOARES

Letters to the Editor

CHART NOTES FROM OUR READERS

About Face

In the Autumn 2012 issue of *Harvard Medicine*, the "BackStory" section shows three facial moulages made during World War I by Varaztad Kazanjian '21. At first glance, there seems to be an incongruity. World War I ended on November 11, 1918. How could Kazanjian have been performing such surgery years before he became a physician?

The answer can be found in the fact that Kazanjian was first a dentist, a 1905 graduate of Harvard Dental School, which closed after World War II.

From the beginning of the Great War in 1914, the British Royal Army Medical Corps had trained hundreds of dentists in the basics of plastic surgery so that they could incorporate their familiarity with facial anatomy, dental occlusion, and prostheses into surgical reconstructions of this region of the body. The effort was necessary: Of all treatments for battlefield injuries, those for facial wounds were among the least satisfactory.

When the United States entered the war in April 1917, Army physicians and dentists were placed under the command of their more experienced British allies. Kazanjian went to England for training in plastic surgery and was then sent to a base hospital to treat facial injuries. There, he developed some novel treatment techniques that so improved the outcomes for facial-injury patients that he was sent to many base hospitals in Britain and on the Continent to instruct military physicians and dentists. He thus became widely known.

After the war, Kazanjian entered HMS with the goal of becoming a plastic surgeon. One day during a gross anatomy lecture on the face, some visiting British plastic surgeons entered the amphitheater. Many of them recognized Kazanjian and disrupted the class by calling out his name in greeting, embarrassing Kazanjian, and confusing his classmates who, until that moment, had not known of his accomplishments.

MORTIMER LORBER '52, DMD '50
WASHINGTON, DC

Dental Work

Kazanjian was first a dentist, a 1905 graduate of Harvard Dental School, which closed after WWII.

MORTIMER LORBER '52, DMD '50
WASHINGTON, DC

Care for the Physician

It was a pleasure to be a part of the article "Multiple Choice" in the Winter 2013 issue of *Harvard Medicine*. I've heard from several people, and they want to know more about the science of decision making, including the newest findings on relational dynamics.

I find this encouraging. Perhaps if more faculty and alumni become aware of the newest research in this field, it would be thought of more frequently as a subject for research, curriculum design, and continuing medical education.

It would be valuable to incorporate relational medicine into the current curriculum at HMS and other medical schools. It would teach students new ways of considering the encounter between themselves and their patients. And it would go a long way toward teaching them how to care for themselves, an important skill for physicians in high-burnout specialties.

JOHN LIVINGSTONE '58
PROVINCETOWN, MASSACHUSETTS

Staying in the Game

Last year I celebrated my 60th reunion, an occasion that provided me an opportunity to send a brief questionnaire to my classmates asking them about their professional activities. I thought others might be interested in what these HMS-trained physicians have done as they've aged.

Of the 147 original members of the Class of 1952, 78 were still living—and I received responses from 75 of them. Fifty were retired and not doing anything related to medicine. Some regretted retiring when they might have instead gone part time and done something "productive" for a couple more decades. Others were pleased to be free of a profession they now see as full of interference from the government and insurance companies.

A number now spend time in something related to medicine—teaching, supervising medical staff, or volunteering to visit patients who are shut-ins or who are dying. Many still work about 10 hours per week as physicians, either as clinicians, surgeons, or psychiatrists; as health administrators; as consultants in health-based organizations; or as developers of medical software. Why we do this is probably best summed up by one respondent: "Why stop now, when I am at the top of my game?"

HENRY GRUNEBAUM '52
CAMBRIDGE, MASSACHUSETTS

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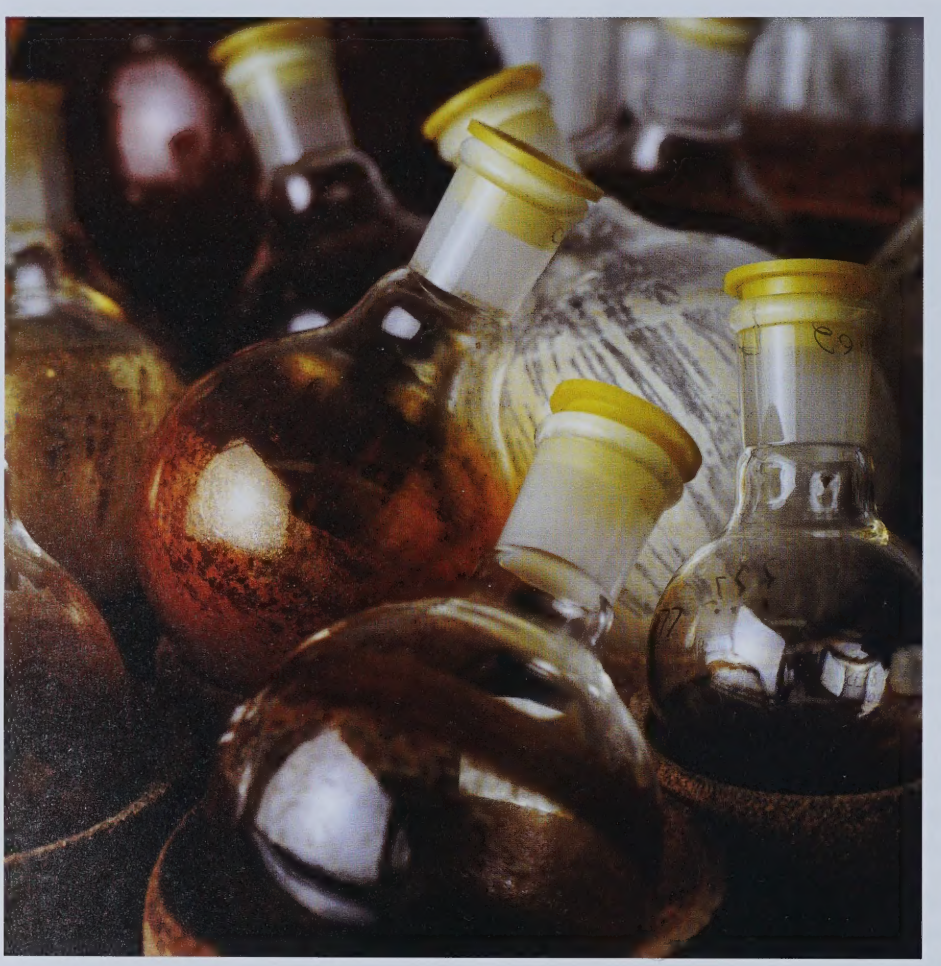
*Harvard Medicine welcomes letters to the editor. Please send letters by mail (*Harvard Medicine, *107 Avenue Louis Pasteur, Suite 111, Boston, MA 02115); fax (617-432-0446); or email (harvardmedicine@hms.harvard.edu). Letters may be edited for length or clarity.*



REINVENTING DRUG DISCOVERY

Cross-disciplinary expertise is key to new therapeutics initiative

THE HARVARD PROGRAM IN THERAPEUTIC Science, or HiTS, a collaborative endeavor aimed at enhancing and eventually leading efforts to reinvent how therapeutic drugs and devices are discovered and evaluated, formally launched in June. Heading this effort is Peter Sorger, the Otto Krayer Professor of Systems Pharmacology at HMS.

Sorger, a leader in the field of systems biology, focuses his research on pathways that control life-and-death decisions in human cancers by incorporating both experimental and computational biology.

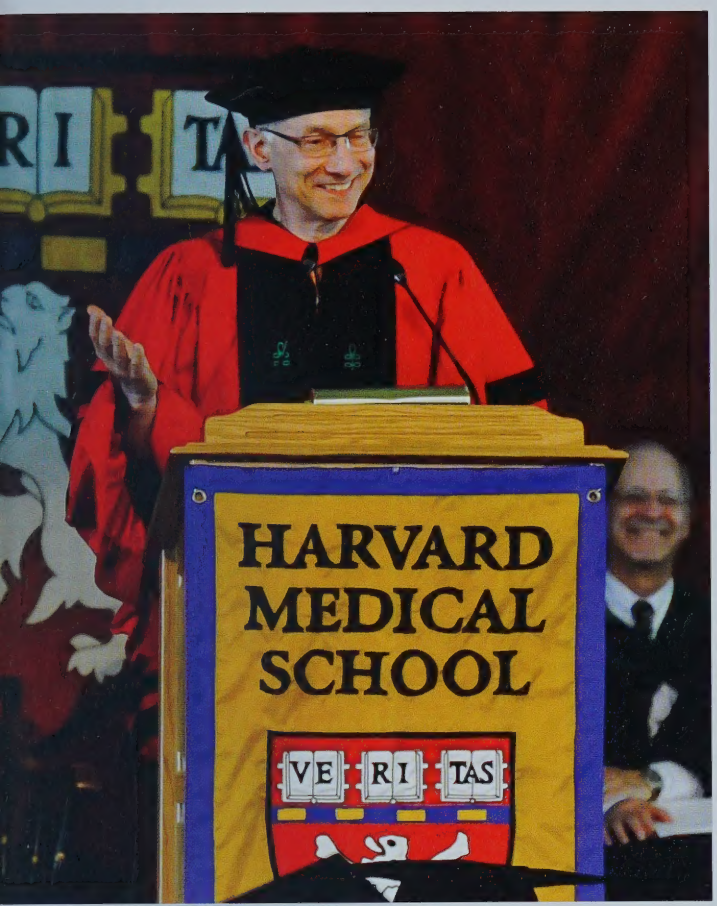
Joining the leadership team is Laura Maliszewski, executive director of HiTS. Marc Kirschner, chair of the HMS Department of Systems Biology and the John Franklin Enders University Professor of Systems Biology, will serve as senior scientific advisor.

"We need a comprehensive approach to rethinking how we go about the most fundamental processes of drug discovery," Sorger says. "The truth is, we simply don't understand how most drugs work, particularly in terms of patient-to-patient variability and the emergence of resistance. In industry, timelines are necessarily too tight and programs too focused to delve deeply into some of the most intriguing therapeutic questions. By contrast, academia is equipped to study basic, open-ended questions and to partner with industry when the ideas are ready for development into actual drugs."

The program will include new research and education programs involving collaborations among HMS and other Harvard schools, HMS-affiliated hospitals and research institutes, the U.S. Food and Drug Administration, the pharmaceutical industry, and other Boston-area universities.

"Therapeutics has been at the forefront of my priorities as dean," Flier wrote in a letter to HMS faculty announcing the launch. "Over the past few years I have been keenly aware of the crisis in the pharmaceutical pipeline, how the vast investments required by traditional pharmaceutical development are not yielding needed therapies, and how a deep solution to this problem will require that new concepts and models be developed within the academy."

HiTS comprises four components: the Laboratory of Systems Pharmacology, with Sorger serving as director, and Tim Mitchison, the Hasib Sabbagh Professor of Systems Biology at HMS, as deputy director; the Therapeutics Technology Cluster, directed by Stephen Blacklow '88, head of the Department of Biological Chemistry and Molecular Pharmacology at HMS, with Caroline Shamu, director of the HMS Institute of Chemistry and Cell Biology, as assistant director; the Program in Regulatory Science; and the Therapeutics Graduate Program, led by David Golan, HMS dean for graduate education.



THE ART OF PRACTICE: In his address to graduating HMS students, Institute of Medicine head Harvey Fineberg emphasized the importance of keeping the whole patient in mind.

PATIENTS FIRST

Class Day speakers remind graduates of their prime directive

ON AN EXCEPTIONALLY WARM spring day under white tents on the HMS Quad, the members of the School's Class of 2013 were showered with waves of applause, and oohs of tenderness for the children some held, as they accepted their crimson hoods. Before the graduates switched the tassels on their mortarboards from left to right, however, the day's speakers dispensed advice about the profession they were about to join.

"Put your patients first," said Harvey Fineberg '71, president of the Institute of Medicine, the health arm of the National Academy of Sciences. "If you do, everything else will fall into place."

Fineberg warned the graduates that putting patients first wouldn't always be easy. Now more than ever, he said, patients come to doctors armed with research and questions. Information and education, however, may not be enough to prepare new doctors for those questions. Although precision medicine—the ability to better match treatments to individuals—will no doubt improve care, the practice of medicine requires more than that, Fineberg told the graduates.

"No matter how molecularly dissected your patient is, no matter how much information you have to offer, keep the whole patient before you," he said.

Class of 2013 members Nina Vasan and Deep Jayendrakumar Shah also addressed those assembled. Shah's speech in particular reflected Fineberg's core message. In telling the story of how, as an HMS student, he had unexpectedly become fearful of taking risks, Shah wondered aloud why students like himself—the cream of a hyperachieving crop—had become risk averse. He then told of an important lesson he learned when one of his mentors described what it takes to be an advocate for your patients.

It takes "the guts to challenge a broken system, and the courage to risk it all for a patient whom everyone else has given up on.... We must take these same risks, not for the sake of being mavericks, but because our profession demands that we always do right by our patients."

—Elizabeth Cooney and Susan Karcz

A Future in PhRMA

AFTER THREE YEARS in his post as HMS executive dean for research and as the Bertarelli Professor of Translational Medical Science, William Chin '72 is leaving the School to become the executive vice-president for science and regulatory affairs at the Pharmaceutical Research and Manufacturers of America (PhRMA) in Washington, DC. PhRMA is an advocacy organization that supports public policies that encourage the discovery of new medicines by pharmaceutical and biotechnology research companies.

STEVE LIPOFSKY; MARK OSTROW (FAR RIGHT)

A MINUTE WELL SPENT

HMS FACULTY RESEARCHERS tell the world what they do, why they love it, and why it's relevant in *Science Matters*, a series of 60-second videos available on the HMS website. These 14 videos capture scientists talking about what inspires them to look for answers to stubborn problems, to travel an untrodden path, or to see old mysteries in a new way. To view the videos, visit http://hms.harvard.edu/research/science-matters.

THE DAILY DRIVE: Systems biologist Galit Lahav (above) and other HMS researchers share their reasons for pursuing a life of discovery in the video series *Science Matters*.

Research Center to Close

HMS LEADERSHIP has announced that the New England Primate Research Center (NEPRC) will wind down operations over the next two years. Rather than seek to renew a five-year federal grant to continue operating the center, the School has begun to work with the National Institutes of Health (NIH) on a transition plan.

Driving the decision was the fact that the external funding environment for scientific research has become increasingly challenging over the past decade. Recent funding pressures have added uncertainty to this already-challenging fiscal context.

A comprehensive plan is being activated to support faculty and staff transition during the wind-down period of 12 to 24 months. Among the plan's priorities is a staffing strategy that will maintain a high level of care for the animals, ensuring that primates will not be adversely affected by the transition.

The School is also working with the NIH and members of the scientific community on a plan for an orderly transition of the NEPRC research programs, so that the scientific work of the center continues.

JUSTIN IDE/HARVARD UNIVERSITY NEWS OFFICE (FAR LEFT); DANA-FARBER CANCER INSTITUTE

Direct Effects

Key HMS program gets a new director

A NEW CHAPTER HAS BEGUN for the Harvard/MIT MD-PhD Program. Loren Walensky starts work in August as the program's new director.

Walensky, an associate professor of pediatrics at HMS and an attending physician in pediatric hematology/oncology at Boston Children's Hospital and the Dana-Farber Cancer Institute, has deep connections to HMS. He is widely respected as a scientist, clinician, teacher, and mentor. In 2006, he received the HMS Young Mentor Award.

Walensky is well suited to lead the program; he's an innovative researcher who combines chemistry and biology to dissect and target deregulated signaling pathways in cancer, and is a dedicated clinician who cares for pediatric cancer patients.

The Harvard/MIT MD-PhD Program has a long and storied history. Established in 1971, it has graduated 513 students, many of whom are in senior leadership positions at leading medical schools, research institutes, biotechnology and pharmaceutical firms, and other key institutions in the United States and internationally. The program provides the opportunity for students to pursue careers at the intersection of medicine and science and to develop lines of scientific inquiry that could change the course of human health for future generations. The program is critical to the mission of HMS.

FROM SCRATCH

Approach uses itch-specific nerve cells to let in relief

THERE'S ITCH, AND THEN THERE'S ITCH. Research led by Clifford Woolf, an HMS professor of neurology, and David Roberson, an HMS graduate student in neuroscience, has revealed distinct sets of itch-generating neurons that explain why itch therapies often fail, and suggests ways to selectively silence itch.

"We think this has therapeutic implications," says Woolf, director of the F.M. Kirby Neurobiology Center at Boston Children's Hospital.

One day, the sensation that sends your fingernails scrambling over your scalp may open the door to relief. Building on science that uses the heat from chili peppers to unlatch the cellular gates to admit a painkiller, the researchers have shown in mice that a lidocaine-like drug can enter the nerve cells that spark itch and squelch the sensation.

Antihistamines don't always work on itch because most itch is not caused by histamine, the substance that induces hives and other miseries. Eczema, atopic dermatitis, and dry-skin itches are spurred by other irritants, prompting specific nerve cells to send signals from skin to spinal cord that scream, "Scratch!"

In their paper in the May online issue of *Nature Neuroscience*, Woolf and Roberson show for the first time that different nerve fibers sense different kinds of itch.

Woolf came to study itch by way of landmark work on pain that he and others, including Bruce Bean, the Robert Winthrop Professor of Neurobiology at HMS, published in 2007 in *Nature*. The scientists delivered the lidocaine derivative QX-314 into pain-sensing nerve fibers via large pores, called ion channels, in nerve-cell membranes. Capsaicin, the searing component in chili peppers, opened an ion channel that allowed QX-314 to selectively enter pain-sensing neurons.

Roberson is testing topical QX-314 creams in mice.

"We are excited about the possibility that this discovery could one day provide long-lasting relief to people suffering from chronic itch," Roberson says. —*Elizabeth Cooney*

Commercial Break

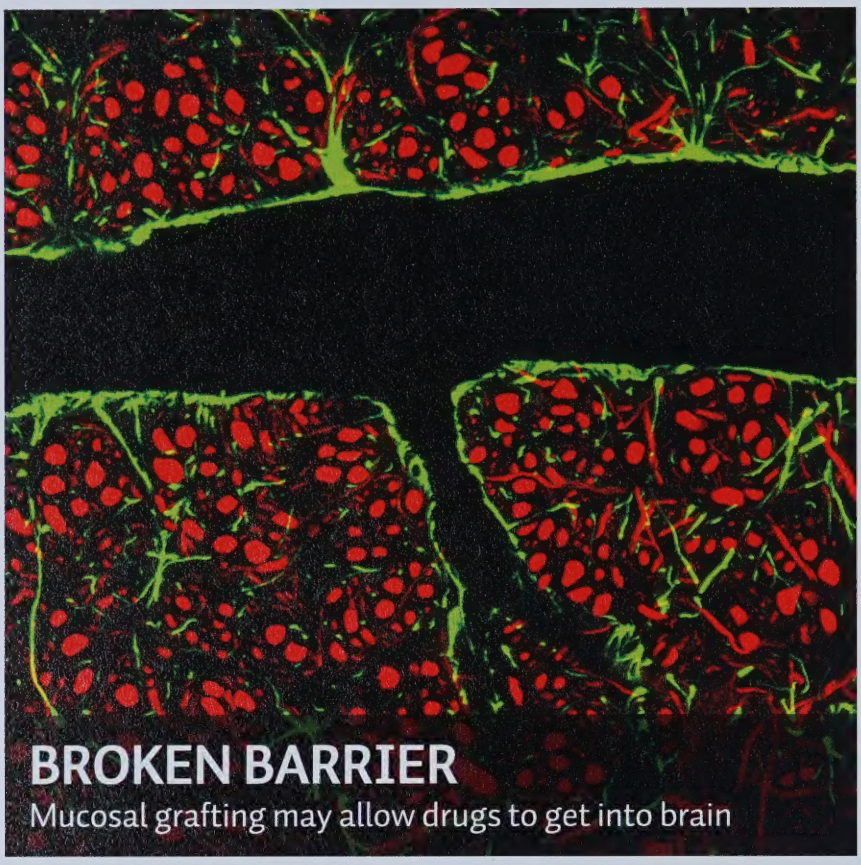
Focus on TV content may hike obesity risk in young

PAYING ATTENTION to what's on television, say HMS researchers, could take a toll on children's health. Investigators at Boston Children's Hospital have shown that being attentive to the content on TV is strongly associated with higher measures of body mass index (BMI) in adolescents. The study, published in the May issue of *Pediatrics*, found no association between BMI and attention to other types of screen media, including video games or computers, despite the duration of use.

"These findings are based on real-time data on how kids are using media in today's complex, multitasking environment," says Michael Rich '91, an HMS associate professor of pediatrics, director of the hospital's Center on Media and Child Health, and the study's senior author. "They indicate that it's the content to which we pay attention and what we do while watching screen media that increase the risk of obesity."

The researchers enrolled 91 teens who were 13 to 15 years old, and measured their height and weight to calculate their BMI. Using a handheld computer, the teens recorded their weekday and Saturday media use, including television, computers, and video games on fixed as well as mobile screens. Participants reported watching TV more than using any other screen media, with an average of more than three hours per day.

"The association between TV and increased BMI may be explained by exposure to TV ads for high-calorie, nutritionally questionable foods, and eating while watching TV, which distracts from natural signals the body gives when it is hungry or satisfied," says David Bickham, an HMS instructor in pediatrics at Boston Children's and the study's lead author.



BROKEN BARRIER

Mucosal grafting may allow drugs to get into brain

IN THE UNITED STATES, more than 20 million children and adults are affected by debilitating neurodegenerative and central nervous system (CNS) diseases. Although multiple drugs exist to treat and potentially cure these diseases, 98 percent of all potential pharmaceutical agents cannot reach the CNS directly: They are unable to cross the blood–brain barrier.

Many attempts have been made to deliver drugs across this barrier using methods such as osmotic disruption and catheter implantation. These methods, however, are temporary and prone to infection and dislodgement.

HMS researchers in the Department of Otology and Laryngology at Massachusetts Eye and Ear have recently demonstrated what may be the first known method to permanently bypass the blood–brain barrier. The method, which uses the lining of the nose as a delivery portal, may offer new treatment options to people with neurodegenerative and CNS disease. The study was published in April in *PLoS ONE*.

Inspired by recent advances in human endoscopic transnasal skull-base surgical techniques, the investigators developed a mouse model of a novel method that used a patient's own tissues to create a semipermeable window in the blood–brain barrier. The researchers then used the model to evaluate whether transmucosal permeability would allow drugs to be delivered directly to the brain.

The scientists showed that the membranes are capable of delivering molecules to the brain that are up to 1,000 times larger than those excluded by the blood–brain barrier.

"Since this is a proven surgical technique known to be safe and well tolerated, these data suggest that these membranes might be used to permanently bypass the blood–brain barrier using a patient's own tissue," says Benjamin Bleier, an HMS assistant professor of otology and laryngology at Mass Eye and Ear.

"Future studies," Bleier adds, "will be directed toward developing clinical trials to test this method in patients who have already undergone these endoscopic surgeries."

—Mary Leach

Jump Start

Genetic mutation linked with precocious puberty

PUBERTY CAN BE TOUGH enough when it occurs in due course, but reaching puberty at an unusually early age can be devastating. Social and psychological development are yet unformed, and lifelong health risks, such as diabetes, breast cancer, and heart disease can result.

A genetic mutation that leads to a type of premature puberty known as central precocious puberty has been identified by researchers at Brigham and Women's Hospital, together with scientists at Boston Children's Hospital, the Broad Institute, and the University of São Paulo, Brazil. Central precocious puberty is defined by the development of secondary sexual characteristics before eight years in girls and nine years in boys.

The study appeared online June 5 in the *New England Journal of Medicine*.

The researchers looked at gene sequencing data in 40 individuals from 15 families with central precocious puberty. In five of the families, they identified four mutations in the *MKRN3* gene that codes for a protein called makorin RING finger protein 3, which is thought to help tag other proteins for degradation. The genetic mutations resulted in truncated proteins and the disruption of protein function. A mutation in the *MKRN3* gene can lead to premature activation of reproductive hormones in the body, thereby initiating early puberty.

The researchers also found that all affected individuals inherited the mutations from their fathers. Moreover, the *MKRN3* gene is located on the same chromosome as genes for Prader-Willi syndrome, a rare condition that results in short stature, incomplete sexual development, cognitive disabilities, insatiable appetite, and severe obesity, among other abnormalities. *MKRN3* is not, however, thought to contribute to the clinical features of Prader-Willi syndrome.

"These findings will help us understand what controls the timing of puberty," says Ursula Kaiser, an HMS professor of medicine and chief of the Division of Endocrinology, Diabetes, and Hypertension at Brigham and Women's. "They also could allow doctors to diagnose the cause of precocious puberty in a subset of patients, or to identify patients at risk for developing precocious puberty."

C.J. GUERIN, PHD, MRC TOXICOLOGY UNIT/SCIENCE SOURCE

ISTOCKPHOTO.COM

Weed Control

Marijuana use may improve insulin resistance among those with diabetes

MARIJUANA (*CANNABIS SATIVA*) has been used for centuries to relieve pain, improve mood, and increase appetite. A synthetic form of its active ingredient, tetrahydrocannabinol, has already been approved by the U.S. Food and Drug Administration to treat the side effects of chemotherapy, AIDS-induced anorexia, nausea, and other medical conditions. With the recent legalization in two states of recreational marijuana use, and the legalization of marijuana for medical use in 19 states and the District of Columbia, physicians will likely encounter new therapeutic uses among their patient populations.

According to a study in the July issue of *The American Journal of Medicine*, one such use may be for patients with diabetes. According to HMS investigators at Beth Israel Deaconess Medical Center, the use of marijuana may help such patients better control their disease.

A multicenter research team led by Beth Israel Deaconess scientists analyzed data from more than 4,500 patients who had participated in the National Health and Nutrition Examination Survey, conducted between 2005 and 2010. The data included fasting blood levels of insulin and glucose and insulin-resistance measures, calculated using the homeostasis model assessment of insulin resistance (HOMA-IR).

"Previous epidemiologic studies have found lower prevalence rates of obesity and diabetes mellitus in marijuana users compared to people who have never used marijuana. But ours is the first study to investigate the relationship between marijuana use and fasting insulin, glucose, and insulin resistance," says lead investigator Murray Mittleman, an HMS associate professor of medicine at Beth Israel Deaconess.

Participants who reported using marijuana in the past month had 16 percent lower levels of fasting insulin, 17 percent lower HOMA-IR measures, and higher levels of high-density lipoprotein cholesterol than participants who reported never having used marijuana. These associations were weaker among those who reported using marijuana at least once, but not in the past 30 days, suggesting that the impact of marijuana use on insulin and insulin resistance is temporary.

—Jerry Berger

Growing Pains

Syndrome describes pain suffered by young people

CHILDREN AND YOUNG ADULTS with widespread chronic pain coupled with other symptoms may suffer from a syndrome newly identified by HMS researchers at Massachusetts General Hospital. Reporting in the April issue of *Pediatrics*, a research team led by Anne Louise Oaklander, an HMS associate professor of neurology and director of the Nerve Injury Unit in the hospital's Department of Neurology, found that most members of a group of young patients had test results that indicated a small-fiber polyneuropathy. This condition had not previously been identified in children. The Mass General investigators call the new syndrome JOSeFINE, short for juvenile-onset small-fiber polyneuropathy.

"We've found the beginnings of a way to better evaluate young patients with otherwise unexplained widespread body pain," says Oaklander. "Identifying tests that are useful for diagnosing this condition could help us reduce the use of unnecessary, expensive, sometimes painful, and potentially harmful testing that many children with these symptoms have undergone."

Small-fiber polyneuropathy involves widespread damage to the type of nerve fibers that carry pain signals from the skin and also control autonomic functions such as heart rate, blood pressure, and sweating. In adults, the disease can be caused by diabetes or other disorders or by exposure to toxic substances. Symptoms include chronic pain in several parts of the body, often beginning in the feet or lower legs; gastrointestinal problems; dizziness or fainting when standing; rapid heart rate; and changes in the skin's appearance.

Many of the 41 patients in the study reported that their symptoms began after an illness or injury. A third had some history of autoimmune illnesses and around half had family histories of autoimmunity. Tests of blood and other body fluids revealed hints of disordered immunity—particularly low levels of a protein involved in the innate immune system.

As a result of their findings, Oaklander's group now takes a two-part approach to evaluating such patients: a determination by a neurologist of the possibility of small-fiber neuropathy, and if that is confirmed, specific blood tests to pinpoint the cause.

—Michael Morrison

Of a Mind

Gene expression can alter with relaxation

RELAXATION PRACTICES can do much more than make you feel refreshed and rejuvenated: They can also elicit a physiologic state of deep rest induced by practices such as meditation and deep breathing. This state, known as the relaxation response, has now been shown to change how certain genes are expressed.

"Many studies have found that mind–body interventions like the relaxation response can reduce stress, enhance wellness in healthy individuals, and counteract the adverse clinical effects of stress in conditions like hypertension, anxiety, diabetes, and aging," says Herbert Benson '61, an HMS professor of medicine and founder of what is now the Benson–Henry Institute for Mind Body Medicine at Massachusetts General Hospital. "Now for the first time we've identified the key physiological hubs through which these benefits might be induced." Benson is co-senior author of the study, which was published in May in *PLoS ONE*.

Benson's team examined changes produced during a single session of relaxation response practice, as well as those taking place over longer periods of time.

The study enrolled 26 healthy adults with no experience in relaxation response practice, who then completed an eight-week relaxation-response training course. Prior to the training, blood samples were taken before and immediately after the participants listened to a health education CD and again 15 minutes later. After completing the training course, a similar set of blood tests was taken before and after participants listened to a CD used to elicit the relaxation response as part of daily practice.

Comparisons of results from pre- and post-training samples revealed significant changes in the expression of several important groups of genes, including those involved in inflammation, energy metabolism, and insulin secretion.

"People have been engaging in these practices for thousands of years," says Benson, "and our finding of this unity of function on a basic-science, genomic level gives greater credibility to what some have called 'new-age medicine.'"

—*Sue McGreevey*

Role Play

Proposed changes to caregiver responsibilities spur debate

INCREASING DEMAND for primary care services, paired with a dwindling supply of primary care physicians in the United States, has some health policy experts calling for more nurse practitioners with greater responsibilities.

In 2010 an Institute of Medicine (IOM) committee recommended that nurse practitioners be allowed to admit patients to hospitals and hospices, lead medical teams and medical homes, and receive reimbursements similar to those physicians receive for providing the same services.

A study published May 16 in the *New England Journal of Medicine* finds, however, that primary care physicians and nurse practitioners significantly disagree on some of the proposed changes to the scope of nurse practitioners' responsibilities.

"We were surprised by the level of disagreement," says Karen Donelan, an HMS assistant professor of medicine at the Mongan Institute for Health Policy at Massachusetts General Hospital and the report's lead author. "We had hypothesized that, since primary care physicians and nurse practitioners had been working together for many years, that collaboration would lead to more common views about their roles in clinical practice. The data reveal disagreements that need to be resolved for teams to function effectively."

Although debates on the appropriate roles of health professionals are nothing new, the authors note that little data have been available on the roles played by nurse practitioners in primary care and how those roles differ from those of primary care physicians. The survey was mailed to a national random sample of nearly 2,000 primary care clinicians—evenly divided between nurse practitioners and physicians—and responses were received from 467 nurse practitioners and 505 physicians.

A majority in each group agreed with the IOM's recommendation that nurse practitioners "be able to practice to the full extent of their education and training." Another point of agreement was that more primary care nurse practitioners were needed to improve access to care.

However, significant disagreement was reported on specific recommendations, including: 82 percent of nurse practitioners believe they should be able to lead medical homes, while 17 percent of physicians agreed; 64 percent of nurse practitioners agree they should be paid equally for providing the same services, compared with 4 percent of physicians; and 60 percent of nurse practitioners in collaborative practices indicate that they provide services to complex patients with multiple conditions, but only 23 percent of physicians in such practices thought those services were provided by nurse practitioners.

JAKE MILLER

VAILLANT EFFORT

Triumphs of Experience: The Men of the Harvard Grant Study
by George E. Vaillant '59
(THE BELKNAP PRESS OF HARVARD UNIVERSITY PRESS, 2012)

reviewed by Elissa Ely

EVERY ONCE IN A WHILE, driven by the need for results, I read a book backward. Usually these are books of the life-assistance variety, especially those offering a path to a more contented state. In such cases, I flip immediately to the conclusion. One wants to get on with it.

The title *Triumphs of Experience: The Men of the Harvard Grant Study*, by George E. Vaillant '59, just about leads the reader by the hand to the last chapter. This is the next in Vaillant's series of looks at the famous Harvard Grant Study, which has been funded almost continuously for 70 years. There is still much he wants you to know.

The 64 Harvard sophomores who were chosen for the study in 1938 because they "were likely to lead successful lives," were eventually joined by cohorts of inner-city men and gifted women. Back then, researchers believed that future leadership could be predicted by body type, a form of head-to-toe phrenology. Physiological and psychological measurements were taken and retaken throughout the years, as personal milestones and professional accomplishments occurred for study members—or did not. It turns out that body type does not predict a successful life.

But what does?

Under Vaillant's more than 40 years of leadership, answers shifted from theories of physical anthropology to those of psychology, then to epidemiology. For this book, he applied what he calls the "decathlon of flourishing" to his 80- to 90-year-old subjects: ten broad, late-life outcomes of occupational, marital, mental, physical, and biological success. For back-to-front readers, here are a few fortifying conclusions: people change and grow (though not inevitably); the impact of trauma lessens with time; and "what goes right in childhood predicts the future far better than what goes wrong." And here are a few surprising conclusions: inner-city men are more prone to chronic medical illnesses, but not those who become college graduates; Democrats have no advantage over Republicans when it comes to marriages, mental health, altruism, or enviable aging; poor maternal relationships are associated with later dementia.

As in his many previous books, Vaillant lets the study members tell their own stories through interviews and writings. Throughout the decades, their lives have provided data for theories of alcoholism, adaptive psychological defenses, and spirituality. Now, their lives are largely behind them. Most speak reflectively, poetically, and, ultimately, reassuringly. "Even a hopeless midlife can blossom into a joyous old age," Vaillant writes.

This book differs from his previous backward glances not only in topic but in perspective. While Vaillant the researcher tracked his subjects around the country and across the globe, Vaillant the man aged along with them. For obvious reasons, he came to view aging as a process of potential instead of pathology and decline. "It's a story about Time—studying it and living in it," he writes. The 32-year-old has become a rueful 78-year-old, looking one more time through his own data, and over his own aging shoulder.

Elissa Ely '88 is a psychiatrist at the Massachusetts Mental Health Center.

NEVERMORE: Controlling the threats of emerging pathogens relies on the coordinated work of local, regional, national, and international surveillance teams. The 1999 outbreak of West Nile virus, first marked by the deaths of winged creatures such as crows and ravens, is an example of the successful coordination of surveillance, warnings, and response. *This painting of a raven is the work of Dallas-based artist Lindsey Kustusch.*

LINDSEY KUSTUSCH; JOHN SOARES (FOLLOWING SPREAD)

A vast network monitors the veiled movements of virulent pathogens

by Shraddha Chakradhar

Under the Radar

In the late summer of 1999, physicians in Queens, New York, confronted something out of the ordinary: patients with encephalitis and muscle weakness—and addresses notably near one another. Doctors were perplexed; there seemed to be no recognizable pathogen associated with the outbreak. Nearly a week after the first cases, and the first fatalities, the New York City Department of Health and the Centers for Disease Control and Prevention (CDC) identified what turned out to be West Nile virus. The news unnerved the infectious disease community: This was the first recorded appearance of West Nile virus in the United States. "I canceled my trip to San Francisco," says Alfred DeMaria '74, state epidemiologist and medical director for the Bureau of Infectious Disease in Massachusetts. "I knew all hell was about to break loose even if the virus wasn't in Massachusetts." ■ And sure enough, the presence of West Nile virus shook, and continues to shake, the nation, with widespread spraying of insecticides aimed at killing virus-bearing mosquitoes and annual warnings urging people to protect themselves from insects carrying the virus.


Alfred DeMaria


Carla D'Addario

In 1999 there were 62 cases and 7 deaths reported. In the years since the initial outbreak, incidence has varied, with 2003 representing a peak; the CDC registered nearly 10,000 cases and more than 260 deaths that year. In 2012, the CDC recorded 5,674 cases of West Nile virus disease, of which 51 percent were neuroinvasive, precipitating conditions such as meningitis or encephalitis. Although the incidence continues to dip, the annual number of deaths has seesawed: in 2012, 286 people succumbed to the disease, more than in the peak infection year of 2003.

In the nearly 14 years since West Nile came ashore, disease surveillance teams in the United States have had to address the appearance of other previously unknown pathogens, from the severe acute respiratory syndrome (SARS) virus of a decade ago to the new strains of influenza viruses that develop annually. While threats of fast-adapting and hard-to-stop bugs are common, what keeps the nation's public health infrastructure from being overwhelmed is the information exchanged through an intricate and efficient network of physicians, infectious disease researchers, epidemiologists, and public health officials who survey, identify, and, when necessary, respond to emergent threats.

Who Are You?

The CDC and global health agencies such as the World Health Organization (WHO), as well as state and local public health units, have developed tools to monitor the spread of infectious disease. The WHO, for instance, supports the use of WHONET, a software project begun by Thomas O'Brien '54, an HMS associate professor of medicine at Brigham and Women's Hospital, and developed and distributed by John Stelling '91, an HMS instructor in medicine at the hospital. The two researchers codirect the WHO Collaborating Centre for Surveillance of Antimicrobial Resistance.

WHONET changed the face of public health and disease surveillance by leveraging existing routine information resources available in microbiology laboratories worldwide.

"Doctors used to send samples to microbiology labs, which would then send the test results to public health departments," says Stelling. "So public health officials would often know about a disease before doctors would."

With WHONET, authorized users in more than 100 nations contribute to local, regional, and international databases for tracking microbial populations, including information on bacterial, fungal, and parasitic pathogens isolated in hospitalized and community-dwelling patients. This level of monitoring allows clinicians and epidemiologists to stay abreast of trends, point occurrences, and broad outbreaks.

WHONET has, for example, been useful for tracking in real time the global spread of carbapenem-resistant Enterobacteriaceae. The Enterobacteriaceae are a family of bacteria that include *Escherichia coli* and the *Klebsiella* species, normal inhabitants of the human gut. Resistance to the carbapenem family of antibiotics, last-line agents in the treatment of patients infected with multi-drug resistant, illness-causing gram-negative bacteria, is troubling—and often fatal. Of particular concern is that many of these infections are health care associated and attributable to the use of medical devices that raise the risk of infection, such as ventilators or intravenous and urinary catheters.

National Guard

A tool that has long been a touchstone for U.S. physicians and researchers is the CDC's *Morbidity and Mortality Weekly Report*, which highlights disease trends, occurrences, and fatalities based on information collected from state departments of public health. In addition, the CDC houses departments responsible for infectious disease surveillance. Within its Office of Infectious Diseases, for instance, is the National Center for Emerging and Zoonotic Infectious Diseases, which tracks diseases that are passed to humans from animal sources.

The CDC has networks that connect state and regional public health organizations. And it has formed partnerships with the National Association of County and City Health Officials and the Association of State and Territorial Health Officials in order to share near real-time data. Overall, the goal is to maintain effective communication and preparedness at all levels of the public sector.

State departments of public health, in turn, have their own systems that allow clinicians, laboratory personnel, public health workers, and epidemiologists to report and share data. The Massachusetts Virtual Epidemiologic Network (MAVEN) has been the Commonwealth's system since 2006.

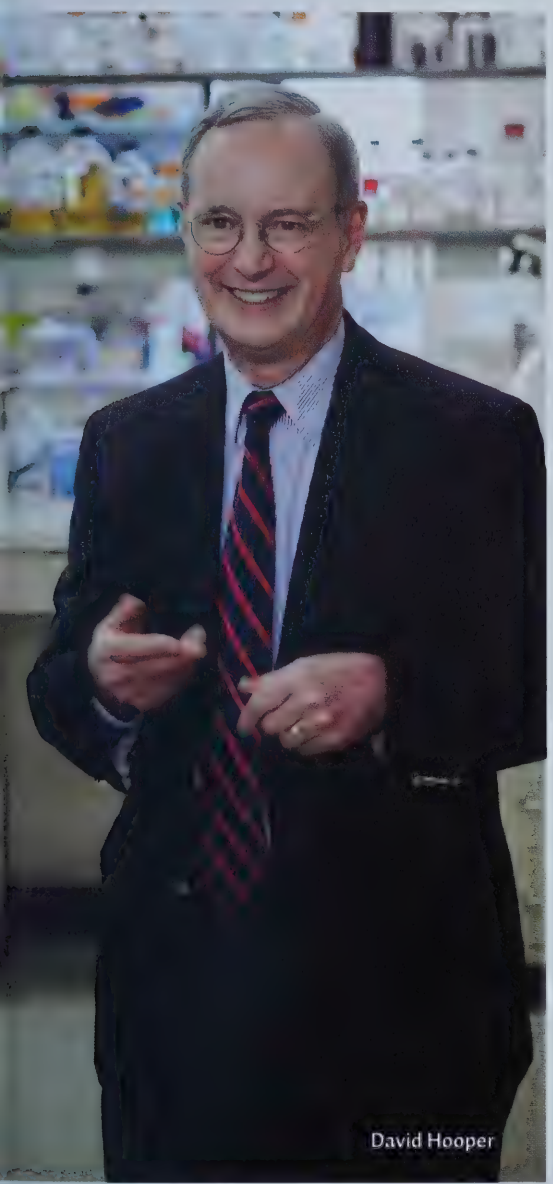
"MAVEN allows public health officials to identify infectious diseases quickly," says DeMaria. "Once the disease has been identified, a public health worker investigates to help prevent its spread."

The system has been instrumental in improving the timeliness of the reporting of hepatitis A infections and, subsequently, the ability of public health officials to identify infected individuals who may be at risk for infecting others. Although MAVEN was developed to meet the specific needs of Massachusetts, other jurisdictions, including Connecticut, North Carolina, and New York City, have adopted the software.

Continental Drift

Although surveillance tools can help identify disease trends, what happens when a patient comes to a hospital with an unidentified illness?

"The first step in evaluation is to consider the history of the patient," says David Hooper, an HMS professor of medicine and chief of the Infection Control Unit at Massachusetts General Hospital. "And in such cases, the person's travel and exposure history and other medical conditions become important. The sicker the patient, the broader the range



It is estimated that hospital-acquired infections affect 1 of every 20 people admitted to hospitals nationwide.

of things to consider, so a thorough history helps ensure we don't miss something that could help with the diagnosis."

"We also look closely at data from the microbiology lab to help identify the specific pathogens involved," he adds. To illustrate, Hooper tells of a patient who was infected by a strain of bacteria that produces NDM-1, or New Delhi metallo-beta-lactamase-1, an enzyme that renders the bacteria resistant to many antibiotics, including those effective against gram-negative microbes. Many bacterial isolates with this resistance have arisen within populations in India.

A history revealed that the Mass General patient had in fact been hospitalized in India before returning to the United States. In addition, microbiologic analyses quickly identified the strain as one resistant to carbapenem antibiotics and, later, showed it was the NDM-1 "superbug."

Once a resistant pathogen is identified and a treatment regimen initiated, Hooper's focus shifts to containment. "We're worried not only about the spread of a particular resistant bacteria between patients," he says, "but also about the potential for patients to develop a hospital-acquired infection."

It is estimated that hospital-acquired infections affect 1 of every 20 people admitted to hospitals nationwide. These infections include those associated with the use of medical devices. The bacteria that cause them can include methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), and pathogens linked with respiratory infections such as pneumonia. Combating these infections can cost hospitals between $5 billion and $7 billion per year.

In a Lather

"There is a real public health crisis in this country," says Erika D'Agata, an HMS associate professor of medicine at Beth Israel Deaconess Medical Center, "because since the 1970s, only three completely new antimicrobials have been introduced to market."

D'Agata develops computational models that devise scenarios for controlling the rate of hospital-acquired infections. "We ask questions like, 'What would happen if we decreased the use of antibiotics?' or 'What if everyone complied with handwashing guidelines?'"

One study by D'Agata found that compliance with handwashing guidelines among health care workers in a particular dialysis unit was approximately 40 percent. The corresponding rate of VRE in that unit hovered near 12 percent. A simulation by D'Agata, however, showed that 100 percent compliance would reduce that prevalence to 2.5 percent.

In order to focus on ways to judiciously use antibiotics, hospitals have begun to participate in antibiotic stewardship programs that monitor the use of the drugs. Driven by data provided by microbiology labs within the hospitals, the programs allow hospitals to monitor, analyze, and improve the ways antibiotics are used. Says Hooper, "We start collecting samples from the patient before anything is administered so we can ensure that the best treatment is chosen and so we can follow the trajectory of the disease and the patient's response to treatment."

Outside the Box

A concrete building in Jamaica Plain, Massachusetts, houses a welter of microbiology labs, each with technicians who monitor, identify, and record the movement of pathogens into and out of the Commonwealth.

"It's the reports from these lab workers," says DeMaria, "that help public health officials identify and investigate outbreaks and respond to them."

The expertise of the laboratory personnel strengthens the surveillance system, more so because they communicate daily with epidemiologists. This type of exchange among clinicians and other relevant parties, says DeMaria, is also what makes the West Nile outbreak such a good example of the public health system at work.

"When we are doing our jobs well, you won't even know we exist," he says. "Pandemics and epidemics are inevitable. But how quickly we get to the bottom of them depends on how well we maintain this network of medical and public health professionals." ■

Shraddha Chakradhar is a science writer based in Boston.

Scientists get pathogens to spill their secrets **by Elizabeth Cooney**

Public Enemies

Invisible invaders have long lived among us. Bacteria, viruses, and parasites have had an upper hand as agents of sickness and death for much of our joint existence. ■ In sickrooms and on battlefields, antibiotics vanquished bacteria only in the past century. The victory seemed sweeping and miraculous. It was, however, short-lived: Bacteria are resilient pathogens that mutate to survive challenges to their well-being. Replicating every 20 minutes, these microbes have proven to be quick-change artists adept at thwarting drugs that target their weak points. ■ Viruses are equally mutable, although it is their genetic infidelity that makes them so slippery. A person infected with the human immunodeficiency virus (HIV) may carry multiple versions of the original virus, copies whose genetic makeups differ so markedly that no single drug can recognize them all. ■ Parasites, including the insidious *Plasmodium falciparum*, which causes malaria, evolved with humans in order to survive. We know this because they've left their fingerprints on our genome.

MATTIAS PALUDI

DISCRETE ELITE: For more than three decades, Bruce Walker has studied patients known as "elite controllers," individuals who become infected with HIV but remain healthy without treatment.

JUSTIN IDE/HARVARD UNIVERSITY NEWS OFFICE

All

told, antimicrobial drug resistance strains budgets and threatens some of the greatest successes in global health. In the United States, for example, treating antibiotic-resistant infections costs $20 billion per year.

Worldwide, up to one in five people diagnosed with HIV infection harbor a strain that is resistant to antiretroviral therapy, now the standard of care. Even antiviral drugs aimed at seasonal influenza are losing their punch, unable to topple influenza A.

Progress against malaria, which causes nearly one million deaths each year—90 percent of those among children in Africa—is hampered by emerging resistance to the only available antimalarial drug. The story is similar for tuberculosis: more than 50 countries have reported cases of extensively drug-resistant tuberculosis.

A new breed of researchers has emerged to counterattack the resistance efforts of these changeable microbes. Scientists are finding ways to reanimate so-called wonder drugs and to develop new technologies that reveal genetic vulnerabilities. These investigators peer back into evolutionary history and trace forward the microorganisms' escape routes to discover ways to eradicate the pathogens and the infectious diseases they cause. But that's not all. These investigators also seek to apply the lessons learned from a given pathogen to other microbial foes that evade our immune defenses.

In the Pink

For Bruce Walker, the challenge is HIV and the unusual patients called "elite controllers," untreated patients who live with only trace

levels of the virus that causes AIDS. He looks beyond the global pandemic.

"I think HIV is giving us a window into the immune system," says Walker, an HMS professor of medicine at Massachusetts General Hospital and director of the Ragon Institute. "If we're talking about the future of medical interventions, I think the next decade is going to show incredible progress in terms of harnessing the immune system to prevent and cure human diseases."

Research has produced drug cocktails that keep HIV infections in check. Scientists generally agree that combination therapies will likely be necessary to fend off other pathogens, too. As an example, Suzanne Walker, an HMS professor of microbiology and immunobiology, points to a once-successful group of antibiotics known as beta-lactams, which have been disarmed by a bacterial stratagem. Beta-lactams act by targeting the bacterial cell wall, disrupting how a cell divides, and disabling the way it grows and establishes an infection. To foil such attacks, bacteria that were once sensitive to beta-lactams changed; they became able to produce an enzyme that chews up the antibiotic before it reaches its target. How to reestablish beta-lactam's effectiveness? One approach: create a drug that blocks the drug-eating enzyme. Once the enzyme is rendered ineffective, the first-line antibiotic works again. This, says Walker, is the strategy behind the composition of Augmentin, the pink liquid known to any parent with a child prone to ear infections. It combines beta-lactam with a defense against the aggressive enzyme.

Envelope, Please

Although rebooting beta-lactam by disabling the disruptive enzyme is effective against mild infections such as sinusitis, pneumonia, and bronchitis, it doesn't faze tougher ones, such as MRSA.

Methicillin-resistant *Staphylococcus aureus*, named MRSA after the antibiotic it deflects, is one of the most virulent pathogens to plague hospitalized patients. Its facility in developing resistance has allowed it to evade all major classes of antibiotics. Suzanne Walker studies the cell envelope of *S. aureus*, the first line of defense for the organism, but also a point of vulnerability.

In their search for a way to target MRSA, Walker's research team screened genes and proteins in *S. aureus* cells to understand steps along the resistance pathway—and to then find compounds that might work against another target. Together with scientists at the HMS Institute of Chemistry and Cell Biology–Longwood Screening Facility, Walker's team singled out an effective chemical compound. A pharmaceutical company is now testing that compound along with other drug candidates that hit the same target.

"If you combine any one of these compounds—including ours—with beta-lactams, they overcome methicillin-resistant infections in animals," Suzanne Walker says. "That's pretty good."

Walker is cautious when she talks about her lab's discovery, pointing to the long history of short-lived successes in our battles against infectious diseases. A footnote to that history, in fact, proved pivotal to her decision to become a chemist. When Walker was nine years old, she heard it was possible to die from a hangnail that had become infected.

"I realized that little things used to kill people," she says. "That was when I learned that antibiotics had not always existed."

That revelation propelled Walker to study biological pathways and to pursue new ways to target infectious disease pathogens.

Capable of targeting bacteria in highly specific ways, phages have evolved in step with the bacteria they infect and consume. Yet they do not harm human cells.

Particle Field

For Tim Lu '10, the eye-opening career moment hit when he was a medical student on rotation at a VA hospital. He was struck by the number of chronic wound infections he was seeing and by the fact that patients returned again and again, never cured.

Lu, an assistant professor of biological engineering and electrical engineering at MIT, looked backward for innovation and found it in an area of biology and infectious disease study that had been shelved for nearly 80 years. He became fascinated by bacteriophages, viruses that were first identified in the early twentieth century. Capable of targeting bacteria in highly specific ways, phages have evolved in step with the bacteria they infect and consume. Yet they do not harm human cells.

More than a century ago, scientists sought to capitalize on this benevolence in studies that attempted to marshal the phages' antimicrobial activity to halt bacterial infections in people. Sometimes the phages worked as the researchers hoped; other times

SABETI'S FINCHES: Pardis Sabeti considers the malaria parasite's ability to develop resistance to potentially lethal agents to be an example of 'evolution in action.'

KRIS SNIBBE/HARVARD UNIVERSITY NEWS OFFICE

they didn't. This perceived unreliability caused bacteriophages to fall from favor as potential antimicrobials, a loss of interest hastened by the expanded use of the more broadly effective, and lifesaving, penicillin.

Those early hit-or-miss results, however, stemmed from a trait that now makes the phages relevant, Lu says. Bacteriophages naturally target certain species of bacteria, some narrowly and some broadly.

Bacteriophages have already proven their worth in molecular biology as tools for overproducing targeted genes or for picking out peptides, short chains of amino acids that have specific properties. Lu and others in the field see a wider potential for these small workhorses.

"Phages are a form of personalized therapy," says Lu. "You can tune the bacteria that the phage likes to feed on."

Tuning Fork

Bruce Walker also seeks to fine-tune systems, specifically the human immune system so that it will fight off HIV. He has witnessed how drug cocktails have changed the face of HIV infection since the early days of the epidemic, when he first saw AIDS patients while a resident at Mass General. After more than 30 years as a researcher in the field, Walker says, "HIV is gradually revealing its secrets."

Better knowledge of the malaria parasite's changing genome can contribute to vaccine development and to better diagnostics. This knowledge can also be used to track which mutations lead to drug resistance.

Among those secrets are the rare individuals who become infected but whose immune systems do not become overwhelmed by a high viral load. Some such people have been infected for more than 30 years and remain healthy without treatment. Scientists have learned that these elite controllers possess a genetic variation that keeps HIV at bay, holding it harmless in reservoirs within their bodies.

The same variation is also associated with a heightened risk for autoimmune diseases, kicking immune systems into high gear and making individuals vulnerable to disorders that cause the body to consider its own tissues to be foreign invaders, marked for destruction.

"The same thing that helps elite controllers potentially fight HIV makes one more susceptible to the cells of one's own body," Walker says. "To understand how it's happening gives us the hope that we might be able to augment immune control of HIV in people who are not controlling it spontaneously."

Drawing on analytic skills more typically applied to stock market movement, computational biologists working with Walker have discovered regions of striking rigidity in the virus—genetic material that has stayed stable in a sea of dynamic mutations. These stable regions might be good therapeutic targets. Other HMS researchers, in collaboration with scientists at Rockefeller University, have isolated potent HIV-neutralizing antibodies from elite controllers.

Knowing how the immune system functions in such powerful ways in some individuals may have broad implications for understanding how the immune system hides disease, Walker speculates.

"We don't yet know how to induce those antibodies, but we do know that the body, under the right circumstances, can make them," he says. "We just have to figure out how to initiate that response with a vaccine."

Fitness Regimen

As with the genetic mutation that confers both HIV control and autoimmune disease risk, changes in genetic character also affect another infectious disease: malaria.

For more than a century, scientists have known that the mutation that causes sickle-cell disease, a red blood cell disorder, also protects people from malaria. This was the first elucidated example of natural selection in humans.


Suzanne Walker

JOHN SOARES

Pardis Sabeti '06, an associate professor of organismic and evolutionary biology at Harvard University, studies genetic variation in the malaria parasite as it occurs through the forces of evolutionary pressure. Like other microbes, the malaria parasite has developed the ability to resist drugs. A program to eradicate the disease, launched in the 1950s, began to fail by the 1970s as the parasite developed resistance not only to chloroquine, the first-line treatment, but also to the insecticide DDT, an agent aimed at mosquitoes that carry the parasite. As each new mutation arose, the parasite evolved; newly mutated forms then spread worldwide. Sabeti calls this "evolution in action"—a demonstration of natural selection occurring in observable time.

"There's a good percentage of the country that doesn't believe in natural selection or evolution, but everybody understands the emergence of drug resistance," Sabeti says. "These microbes are evolving, they're changing, they're developing resistance, and they're spreading. And it's happening all the time."

Malaria is deeply challenging for another reason: the parasite needs humans as part of its life cycle. "Anytime you become a critical part of a microbe's life cycle, it's going to be a far bigger challenge to get it to give you up," Sabeti adds.

Better knowledge of the malaria parasite's changing genome can contribute to vaccine development and to better diagnostics. This knowledge can also be used to track which mutations lead to drug resistance to help inform which treatments to offer which patients.

"We have not exhausted our ability to get more information from understanding our defenses against malaria," Sabeti says. "The more we understand how these microbes use their own diversity to their advantage, the better off we will be in our development of treatments, vaccines, and surveillance capacity."

Suzanne Walker hedges when asked if she is hopeful about taming antibiotic resistance.

"I'm not unoptimistic, so long as people think differently about the problem. We need to take a variety of approaches and explore novel ideas," she says.

The microbes—in all their diversity and novelty—won't wait. ■

Elizabeth Cooney is a science writer in the HMS Office of Communications and External Relations.

Humans and the life forms they host are in it together **by Susan Karcz**

MATTIAS PALUDI

You are a walking ecosystem. And you are not alone. Ever. ✹ Microbial life teems on, and in, your body. If you're healthy, these life forms live in harmony with you in a stable and balanced system, where host and guest alike contribute to the rhythm and hum of a cooperative community. ✹ Humans and microbes have coevolved to a point of mutual benefit—we need each other. The number of microbial cells in our bodies outstrips the number of human cells by about ten to one. And while the human genome contains approximately 30,000 genes, the microbial genome, the microbiome, is made up of more than four million genes. We are more "them" than "us." ✹ There's a growing interest in studying the ecosystem that is the human microbiome, and it's more than a research trend. It may herald a shift in how we think about human health and medicine and our place in the natural world.

cottage industry

Compartment Living

The human microbiome comprises organisms and their genomes—bacteria, viruses, fungi, and other single-celled eukaryotes—that occupy several body habitats: the gut, mouth, nasal passages, vagina, and skin. Each of these habitats features organisms, collectively the microbiota, that have adapted to, and even shaped, their particular niche. Not only is the mix of microbes living in the gut different from that on the skin, but there are microhabitats within habitats. The microbiota just inside your nostril, for example, differ from those living deeper in the passageway inside the sinus cavity. And that's not all. The continual interplay between a person's genetic makeup and the surrounding environment also influences how a microbiome is populated.

A healthy microbiome is highly diverse, stable, and resilient: diverse, in order to avoid species domination and to provide a wide set of functions; stable, in order to keep body functions running smoothly; and resilient, in order to recover from the inevitable assaults. Disturb it and it will likely recover, but it will never be the same.

The microbes that live with us are active community members. And as you might find in any community, some members contribute to the greater good, some remain neutral, and some may become harmful given certain conditions. Among other functions, microbes help digest and extract nutrients from food, regulate metabolic processes, guide immune system responses, and protect against invasions by pathogens. In a healthy person, the beneficial bacteria help create a stable environment that promotes and protects the health of the human host.

In fact, these microbes adapt to, and perhaps even determine, the biological properties of the human host. David Relman '81, the Thomas M. and Joan C. Merigan Professor in the Departments of Medicine and of Microbiology and Immunology at Stanford University and chief of infectious diseases at the VA Palo Alto Health Care System in California, describes the microbiome as a "complex set of communities of microorganisms that have chosen the human body as their home and that operate as a unit, as most communities do. By doing so, they are furthering their own beneficial purposes, both for themselves and for their host."

Home Grown

The microbial species that call us "home" operate in a symbiotic relationship with their hosts in an ancient contract revised over eons of coevolution. In this mutually beneficial system, humans provide food and shelter while the microbes provide protection from harmful invaders and help with essential body functions.

Infants are born with almost no microbiota: They acquire some during birth, although the mix and type of microbes differ depending on method of delivery. Babies born vaginally acquire microbiota from their mothers during the trip through the birth canal, whereas babies born by cesarean delivery receive their introductory dose of microbiota from contact with their mother's skin. This first exposure is the initial step in developing an immune system and helps determine the composition of an infant's microbial community. These early differences diminish in importance as other influences, such as diet, health, and geographic location, begin to hold sway and shape a child's microbiome.

A microbiome can also assemble, or reassemble, after a disturbance, such as treatment involving an extended or repeated courses of antibiotics. Such therapy may well eradicate a targeted pathogen but, as collateral damage, also knocks out some of the beneficial or benign microbiota. If the community is resilient, the microbiome may return to its pre-disturbance state, but this recovery takes time and is far from guaranteed.

And, under the right conditions, an invasive pathogen can take advantage of a vulnerable community to gain a foothold in, or attempt to colonize, the host. Part of the microbiome's responsibility is to help defend its host from pathogens by making surface environments inhospitable to invading species, a process referred to as "colonization resistance."

"The particular difficulty for organisms that don't normally live with us, ones that are actually pathogens from the outside world," says Katherine Lemon '01, an HMS assistant professor of pediatrics at Boston Children's Hospital and the Forsyth Institute, "is that they not only have to deal with our defenses, like our immune system, they also have to come into an established microbial community."

ANNIE TRITT PHOTOGRAPHY (FAR LEFT); JOHN SOARES

INSIDE JOB: Researchers David Relman (far left), Dennis Kasper, and Katherine Lemon study the intricacies of our relationships with the legions of microbes that live within and on our bodies.

JOHN SOARES

While the immune system can generally withstand such assaults, if the pathogen is especially aggressive or plentiful, the invasion may succeed and alter the mix of microbiota.

"Understanding the means of microbiome assembly," says Relman, "is key to managing pathogen invasions and to thinking of human health as a collective property of the human body and its associated microbiome."

Balancing Act

The immune response presents a formidable defense, and if the response subsides after a threat has passed, all is well. Sometimes, however, the response continues without reason, a characteristic of autoimmune disorders such as Crohn's disease, ulcerative colitis, multiple sclerosis, psoriasis, type 1 diabetes, and asthma.

In the United States and other developed countries, the incidence of autoimmune diseases has been on the rise over the past 30 to 40 years, a situation some experts attribute to changes in the microbial balance in humans. A number of factors, such as overuse of antibiotics and of hormones, both in the animals we eat and in therapeutics, have, according to Dennis Kasper, William Ellery Channing Professor of Medicine and an HMS professor of microbiology and immunobiology, "affected the microbiome and caused a shift so that now we don't have the organisms that were properly balancing our immune system and preventing us from getting some of these diseases."

Ebbs and flows in the balance of an individual's microbiota may help explain the cyclic nature of some autoimmune diseases in humans. But it's not just that gut bacteria become imbalanced. "You also have to have a genetic susceptibility," says Kasper. "The fact that the bacteria become imbalanced, and you're genetically susceptible, can partly explain why conditions like multiple sclerosis occur in individuals and why the diseases are relapsing and remitting in nature."

People living in developed countries may be becoming less dependent on coevolved gut microbiota. Some researchers, including Kasper, think that the increase in autoimmune disorders, sometimes called microbiome-based disorders, could be a consequence of the greater vulnerability of the host–microbiota relationship partly caused by trends such as eating highly processed foods and living in overly hygienic environments.

Seed Catalog

Ecological models have long used the metaphor of a symbiotic, mutually beneficial, and dynamic community to frame discussions of the degree of ecosystem health. The idea of the human body as an ecosystem is gaining traction in microbiome research, with human health being viewed as a "service" delivered in part by resident microbiota.

"All you have to do," says Relman, one of the principal proponents of this concept, "is borrow the language of ecologists and read their literature, and suddenly you're looking at the world in a very different way. And the implication of that new perspective for medicine is that we are going to have to develop a whole different set of tools dedicated to restoring and maintaining the beneficial properties of the microbiota."

Some of these future tools may include using environmental perturbation as a therapy. You could, says Lemon, "introduce an organism and use it to create a colonization blockade, where you have a harmless organism occupy the same niche as a harmful one, for instance, *Staphylococcus aureus*. And allow the harmless one to take hold." This replanting and reseeding approach is microbiota management—stewardship to promote human health.

Fecal transplantation, another example of replanting and reseeding, is being used in humans now, although only in people who are sickened by recurrent *Clostridium difficile* infections. Although it has enjoyed some success, Kasper says that "the problem with probiotics or fecal transplants is that the introduced organisms will potentially still be there after the disease has ended. And we don't know what their long-term effects are."

Microbiome research is in a honeymoon period, when the excitement of discovery peaks. There is a luster to the symbiosis between humans and our resident microbiota that many hope will be burnished rather than tarnished as researchers gain a better understanding of how human health is affected by our own actions and those of our nearest neighbors. ■

Susan Karcz is assistant editor of Harvard Medicine *magazine.*

The fight against

infectious diseases increasingly links discovery with care by Jake Miller

Epidemic Proportions

When *Mycobacterium tuberculosis* invades a person's body, it doesn't just settle into the lungs and look for a spot from which to eke out a living. It hijacks that person's macrophages—cells that attack invading bacteria—and uses the mechanisms of inflammation to manipulate the environment around it, remodeling its new home to suit its needs. ■ Salmaan Keshavjee knew about *Mycobacterium*'s penchant for makeovers, and thought that this knowledge might be useful in the fight against tuberculosis. So he was intrigued when he learned of an unusual approach that researchers at Sweden's Karolinska Institutet were taking to control these bacteria-orchestrated renovations.

A WAR WITH LITTLE PEACE: The incidence of extensively drug-resistant tuberculosis continues to grow in Russia. This young man is a patient in a tuberculosis ward in a psychiatric hospital in the North Caucasus region of that nation.

Paul Farmer

To understand this twist in the body's normal path of self-defense, and to find ways to get the immune response back on track, the Sweden-based team, led by Markus Maeurer, a professor of clinical immunology at the institute, had cultured the mesenchymal stem cells from patients with extensively drug-resistant tuberculosis (XDR TB), then reinfused the patients with those cultured stem cells. Because mesenchymal stem cells help suppress inflammation, the researchers wanted to see if they could safely dampen and refocus the inflammatory response without compromising immune function.

"Their preliminary data suggested that the stem cells didn't suppress immunity in an adverse way, and surprisingly, the patients who received the transplanted cells did much better on their XDR TB treatment than typical patients in their condition," says Keshavjee, an HMS associate professor in the Department of Global Health and Social Medicine and a physician in the Division of Global Health Equity at Brigham and Women's Hospital. With the treatments now in use, fewer than a third of patients with XDR TB recover, but in this small initial study, all the participants appeared to recover.

Keshavjee is developing a partnership with the institute's team, laying a foundation for more-extensive trials of the treatment in Russia and Peru. "Saving lives from a disease that's killing people—that's always good," Keshavjee says. "But this work also opens the door to thinking about tuberculosis differently. If the mycobacterium is manipulating its environment by modulating T cells and other immune cells, we need to ask, 'What if we unmodulate that environment?' "

"Inside our bodies, the bugs are living in an ecosystem," he adds. "As humans, we also have our own ecology, which plays out in society. Recognizing the complex biosocial nature of infectious diseases moves you toward some crucial insights about how these diseases work and how to fight them."

To fight infectious diseases worldwide, biomedical researchers and clinicians are joining efforts to apply laboratory-based discoveries to the challenge of saving the lives of people with tuberculosis, cholera, and other age-old ravages. These international collaborations are increasingly considering such diseases in context, as integrated parts of complex interconnected systems that involve humans.

"We now have genomic and proteomic platforms that are beginning to have immediate relevance to the challenges of diagnosing and treating infectious disease in poor communities," says Paul Farmer '90, the Kolokotrones University Professor at Harvard, head of the Department of Global Health and Social Medicine at HMS, and a cofounder of Partners In Health, an international nonprofit that brings health care to the poor. "Many of these new technologies are more portable, scalable, and affordable than ever before."

In Black and White

Tuberculosis is a global public health issue that is unevenly distributed: the burden of the disease is highest in Asia and Africa, with India and China accounting for almost 40 percent of cases. Africa has 24 percent of the world's cases and the highest rates of disease and death per capita. In the Russian Federation, XDR TB is a particular concern: it has rapidly spread through prison populations. In Peru, while the incidence of tuberculosis is decreasing, the incidence of multidrug-resistant tuberculosis is on the rise. Overall, according to a 2012 report from the World Health Organization, there were an estimated 8.7 million new cases of tuberculosis and 1.4 million deaths worldwide from the disease in 2011.

Similar sobering statistics can be found for cholera. Although up to 80 percent of cholera cases can be successfully treated with low-cost oral rehydration salts, the WHO estimates that annually more than 100,000 people succumb to the disease.The impact of cholera is most acute in regions with poor sanitation and unsafe supplies of drinking water, conditions that annually spawn three to five million cases worldwide. The entire country of Bangladesh is considered at high risk for this disease, the only country with this designation from the WHO.

Delete Buttons

Like tuberculosis, cholera elicits a complex immune response. The infection takes place in the mucosal membrane of the small intestine, where billions of beneficial bacteria live. Our gut microbiota perform welcome chores such as fermenting carbohydrates to release their useful energy. Although our gut mucosa is always on the alert for foreign bacteria, killing every newcomer would be imprudent, as some may be useful in maintaining the health of their human host. Yet when a pathogen is identified, the mucosal cells mount a vigorous immune response.

Unfortunately, the basic mechanisms of that response are still poorly understood. This knowledge gap has hindered the development of effective, durable vaccines for diseases such as cholera. In fact, current vaccines offer only partial protection that lasts for just a few years.

To extend this protection, or perhaps even block the disease permanently, researchers, including John Mekalanos, the Adele H. Lehman Professor of Microbiology and Molecular Genetics and head of the Department of Microbiology and Immunobiology at HMS, are tweaking the genetic makeup of *Vibrio cholerae*. The trick has been determining how to eliminate

JUSTIN IDE/HARVARD UNIVERSITY NEWS OFFICE; THOMAS DWORZAK/MAGNUM PHOTOS (OPENING SPREAD)

the genes that turn off the disease without disturbing the ones that elicit an immune reaction. Mekalanos, along with Mike Levine at the University of Maryland, has pioneered the use of a live oral cholera vaccine. This vaccine uses a genetically altered version of the organism that is unable to cause disease.

In addition to learning which genes halt the cholera bacterium, it is necessary to understand which ones are activated during its transmission and infection. Stephen Calderwood '75, the Morton N. Swartz, M.D. Academy Professor of Medicine (Microbiology and Immunobiology) at HMS and Massachusetts General Hospital, is looking at gene expression at different points in *V. cholerae*'s life cycle to determine which genes are expressed by the pathogen during infection, as well as which trigger immune responses in the human host.

For this research, Calderwood is collaborating with clinicians and researchers at the International Centre for Diarrhoeal Disease Research in Dhaka, Bangladesh. Calderwood's team has collected thousands of samples from patients who have been hospitalized with severe cholera.

The Sniff Test

The insights from such molecular biology studies can also lead to some surprising diagnostic tools for infectious disease. The tubercle bacterium, for example, can be insidious; it can lurk in the lungs of a mildly infected patient for years. Active infections of the bacterium, however, release a detectable signature of volatile organic compounds. This airborne fingerprint may be useful in diagnosing the disease, particularly in children; not only is it difficult for them to produce sufficient sputum for analysis, their sputum contains relatively few of the organisms.

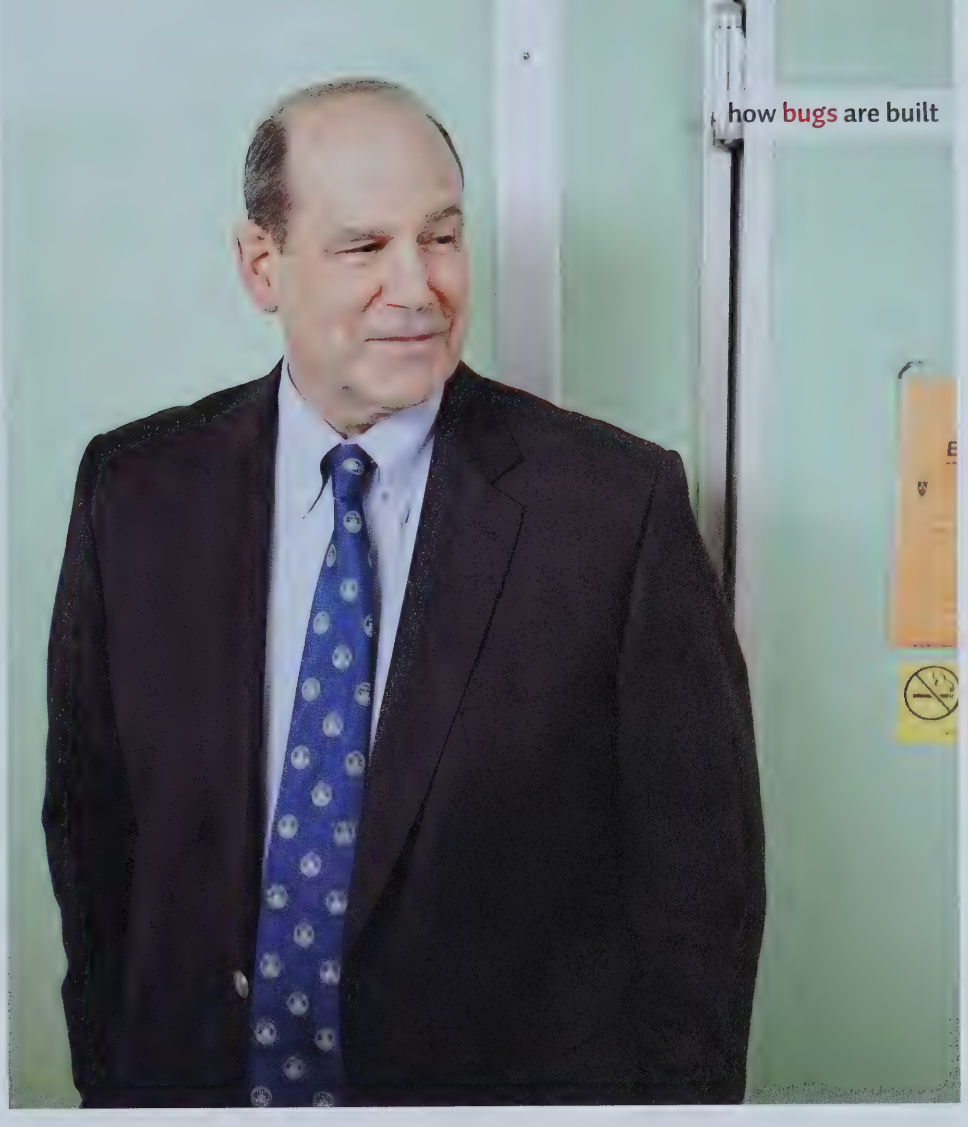
"A baby's exhalation could be captured," says Ed Nardell, an HMS associate professor of medicine at Brigham and Women's, "so she wouldn't need to produce a sputum sample."

Nardell is part of a team that's investigating the effectiveness of a new gas chromatography technology that can detect the chemical signature of *M. tuberculosis* in a few puffs of human breath. In some parts of the world, giant Gambian rats, trained to sniff out the bacterium's signature compounds, are already being used to detect *M. tuberculosis* in sputum samples. Unlike humans using microscopes, these trained rats accurately examine specimen after specimen without fatigue—and all for the fee of a sweet treat.

Phase Shifts

Another complicating factor in the fight against these diseases is that the causal agents change throughout their life cycles. The tubercle bacterium modifies its environment to suit

JOHN SOARES



BENCH EXERCISES: By uncovering the molecular characteristics of the pathogens that cause tuberculosis and cholera, researchers Salmaan Keshavjee (far left), Mercedes Becerra, Ed Nardell, and Stephen Calderwood help inform prevention and treatment efforts worldwide.

JOHN SOARES

its needs. By contrast, the cholera bacterium acclimates itself to the environment it inhabits. Many cholera microbes spend their lives in water, feeding on plankton to derive energy. During this aquatic phase, the adaptations that help them survive in water make them much less infectious in humans. Calderwood and his team, however, have discovered that the cholera microbes found in the fecal matter of infected humans—before the microbes adapt to the aquatic environment—are hyperinfectious for a brief period following their evacuation from the host.

Just as it is crucial to see how the bacteria operate in human hosts, it is important to understand how the illness plays out in the context of human populations.

Because this human ecology is important to the transmission of the disease, Calderwood's collaborators in Bangladesh dispatch research teams to patients' homes. To study disease transmission in a household, the team invites all family members, sick or well, to participate. While visiting, the team can survey a patient's living conditions and, if needed, provide medical care to other family members.

"These diseases are perfect examples of how knowing the social context of an infection can be crucial," says Mercedes Becerra, an HMS associate professor of global health and social medicine. "It's not some vague notion of social context; it's actually seeing the physical setting where people live and testing the strains that have infected different members of a family or community. The household is a really important unit for analysis and for medical interaction."

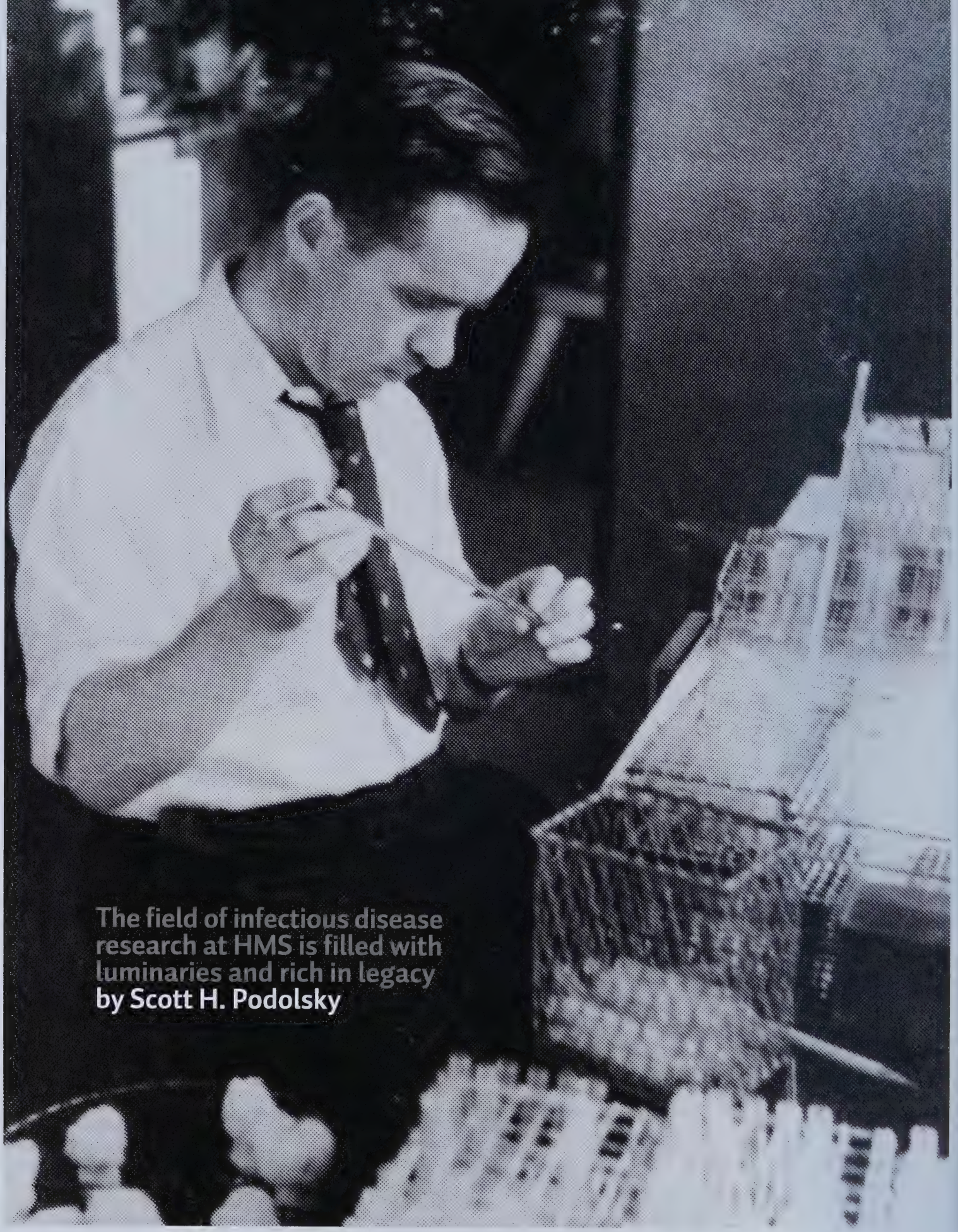
Just as it is crucial to see how the bacteria operate—at the chemical and genetic levels—in human hosts, it is important to understand how the illness plays out in the context of specific human populations, according to Becerra.

Knit One, World View

These diseases also interact in another key ecosystem: the community of HMS researchers working on global health and infectious disease. Some may be community health workers with knowledge of the lives of their neighbors. Some are social scientists measuring the clinical effectiveness of different approaches to preventing and treating these diseases, or mapping the social, political, and historical aspects of health. Geneticists, immunologists, engineers, and architects—each play a role in teasing out the intricacies of these diseases and the pathogens that cause them.

"To beat these diseases, somebody has to understand the immune system and the bugs at different levels," Becerra says, "while others have to work on understanding the impact on patients and families. That's why it's so important to work together from multiple angles, linking discovery with care delivery—and then turn around to look for new discoveries." ■

Jake Miller is a science writer in the HMS Office of Communications and External Relations.

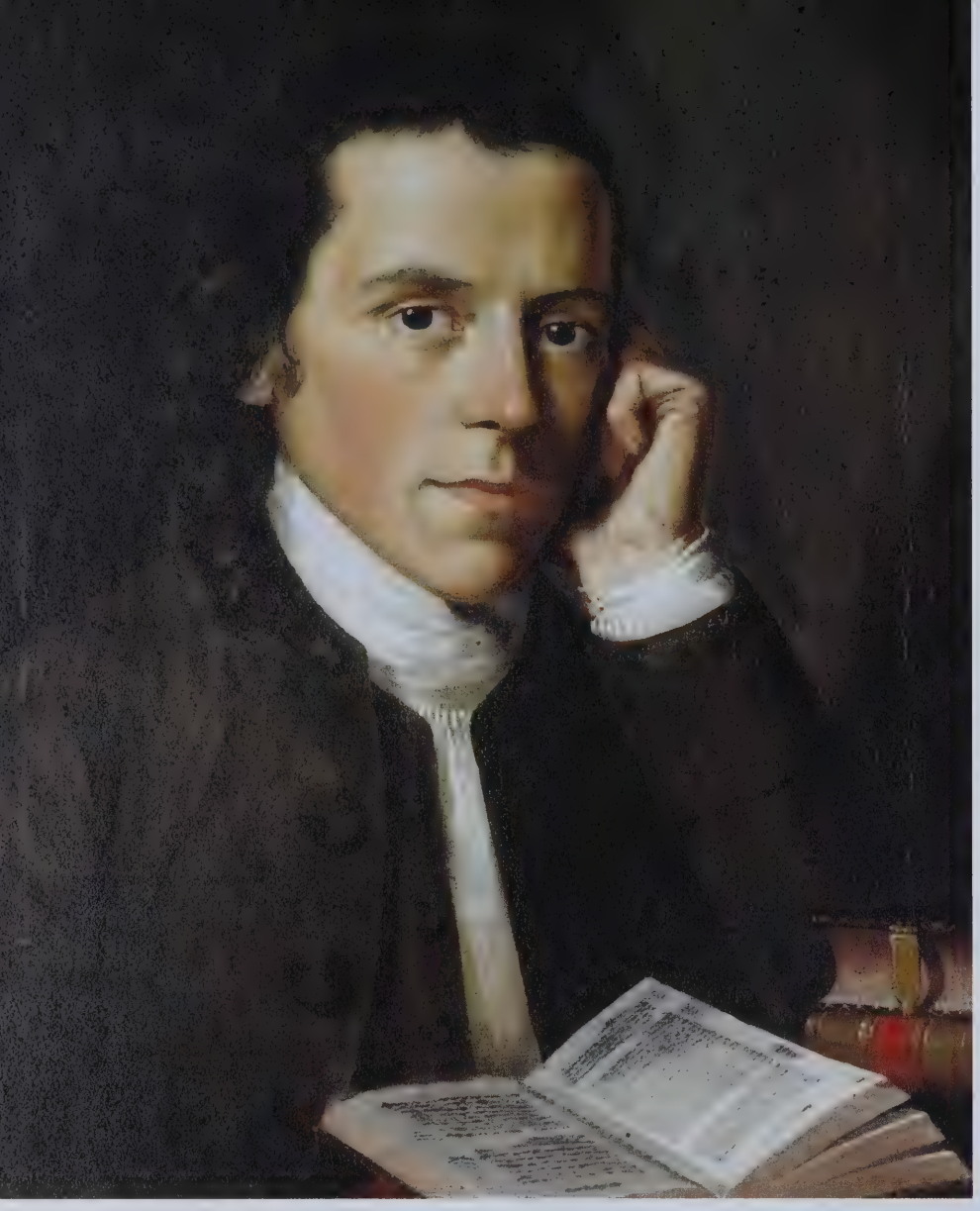


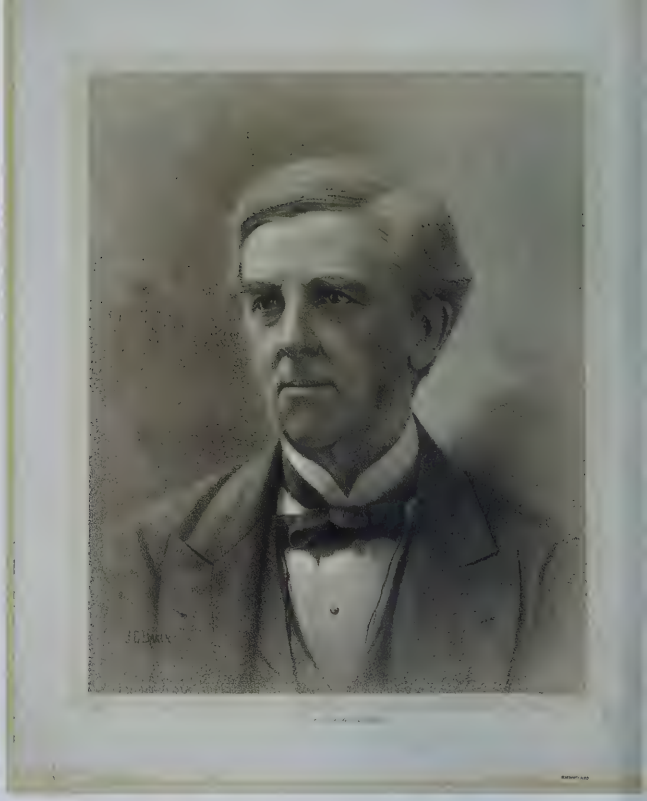
The field of infectious disease research at HMS is filled with luminaries and rich in legacy
by Scott H. Podolsky

FINLAND, MAXWELL. *THE HARVARD MEDICAL UNIT AT BOSTON CITY HOSPITAL/MAXWELL FINLAND*. [CHARLOTTESVILLE]: DISTRIBUTED BY UNIVERSITY PRESS OF VIRGINIA FOR FRANCIS A. COUNTWAY LIBRARY OF MEDICINE, HARVARD MEDICAL SCHOOL, BOSTON, 1982-1983 (OPPOSITE PAGE); FRANCIS A. COUNTWAY LIBRARY OF MEDICINE

to finland and back

For more than two centuries—from the pre-germ theory era, through the antibiotic age, and into recent decades marked by emerging infections and fears of a postantibiotic period—researchers at Harvard Medical School have confronted infectious disease. HMS faculty such as Benjamin Waterhouse; Oliver Wendell Holmes, Class of 1836; and Maxwell Finland '26 have figured prominently in this work, as have Harvard researchers Theobald Smith, Edward Kass, and Nobelists John Enders and Thomas Weller '40. The work by these scientists and others has spanned the spectrum from vaccination and infection control to the rational application of antimicrobial therapy itself.





REDWOOD LIBRARY AND ATHENAEUM, NEWPORT, RI, BEQUEST OF LOUISA LEE WATERHOUSE (MRS. BENJAMIN WATERHOUSE) OF CAMBRIDGE, MA. DIGITIZED AT THE LIBRARY OF CONGRESS (FAR LEFT); OLIVER WENDELL HOLMES BY ARMSTRONG & CO., 1879, LIBRARY OF CONGRESS

The

roots of this interest in infectious disease might be traced to Waterhouse, the School's first Hersey Professor of the Theory and Practice of Physic. Waterhouse trained in London and Edinburgh at the time of the American Revolutionary War. This did not help his application to the Hersey Professorship—both John Hancock and Samuel Adams opposed his appointment—but it did lead to important London connections. Edward Jenner, an English physician, performed his classic smallpox vaccination experiments in 1796, and Waterhouse himself received the vaccine from friends in England in July 1800. His enthusiasm for vaccination, which earned him the nickname "Jenner of America," began at home: Waterhouse performed his first vaccination on his five-year-old son, then on three more of his children and two servants, and later confirmed the vaccine's efficacy by inoculating all of them with smallpox. Waterhouse also supplied vaccine to Thomas Jefferson, who vaccinated his own family members and arranged for the vaccination of members of a Native American delegation to Washington, DC, in December 1801. But Waterhouse later fell from favor at HMS. After antagonizing the Warrens, the Boston family instrumental in the founding and development of HMS as a center for medicine and medical education, he was ousted from the School in 1812 and replaced by Boston physician James Jackson.

Jackson's son pursued medicine in Paris and, sadly, died there of typhoid fever. But before his untimely death, he studied with the young Holmes, of whom the elder Jackson wrote: "Do not mind his apparent frivolity."

When Holmes returned home, he set up shop in Boston under a sign stating, "Small fevers gratefully received." But for all his wit, Holmes was deadly serious when necessary. He was never more so than during his investigations of the contagiousness of puerperal (childbed) fever, conducted and written "in a great heat and with passionate indignation" in 1843. After collecting cases from across New England, Holmes reported his findings to the Boston Society for Medical Improvement, demanding that physicians take care not to spread the pestilence. He advised that those physicians who were linked to two cases of puerperal fever "within a short period" withdraw from the practice of obstetrics for at least a month. Applying his full literary talents to the cause, Holmes angrily concluded: "The woman about to become a mother, or with her new-born infant upon her bosom, should be the object of trembling care and sympathy wherever she bears her tender burden, or stretches her aching limbs.... God forbid that any member of the profession to which she trusts her life, doubly precious at that eventful period, should hazard it negligently, unadvisedly, or selfishly!" Holmes delivered his cautionary statements a full 4 years before Hungarian physician Ignaz Semmelweis conducted prospective studies of the contagiousness of puerperal fever, and 36 years before

LEADING LIGHTS: Early research on infectious disease included that by Benjamin Waterhouse (far left) and Oliver Wendell Holmes. A sundering with the School's founding family led to Waterhouse's dismissal and the hiring of James Jackson.

Louis Pasteur identified the streptococcal bacterium as the agent that causes puerperal fever and erysipelas.

Infectious Personality

Another six decades would pass before sulfa drugs would be used to successfully treat puerperal fever and erysipelas. At HMS, sulfa drugs, and then antibiotics, would be evaluated by Finland, arguably the foremost antibiotic researcher in the world at the time.

Finland had started at Boston City Hospital in the mid-1920s, conducting controlled clinical trials of antipneumococcal antiserum for the treatment of pneumonia. Throughout the next five decades, nearly every successful antimicrobial agent, from sulfa drugs to penicillin and broad-spectrum antibiotics, seemed to require what Robert Petersdorf—himself a renowned infectious disease expert and, at one time, the president of Brigham and Women's Hospital—called the "Finland stamp of approval." In the process, Finland worked to instill caution and rigor in the emerging post–World War II field of clinical pharmacology by demanding objectivity and rigor from investigators.

By any measure, Finland's impact was enormous. He trained more than 100 fellows in infectious diseases, including seven future presidents of the Infectious Diseases Society of America (he served as its first president) and numerous others who would go on to chair infectious disease departments and lead training programs of their own. As his Harvard colleagues remembered: "There were relatively few places in which to train in infectious diseases in the years immediately following the cessation of World War II, and expansion of training programs basically had to wait until his former fellows had risen to prominence."

Finland left other important legacies. He drew early attention to emerging staphylococcal antibiotic resistance, writing in 1951: "No honest or self-respecting physician or surgeon, whether his practice be limited to pediatrics, geriatrics, or any other special field of medicine or surgery, can help but feel a bit conscience stricken each time he prescribes or administers a sulfa drug or antibiotic after a hurried visit to the bedside of a patient or after a brief interview and examination in his office.... Are we in medicine, like our counterparts in industry, exhausting our most valuable resources at too rapid a rate?... Only time will tell."

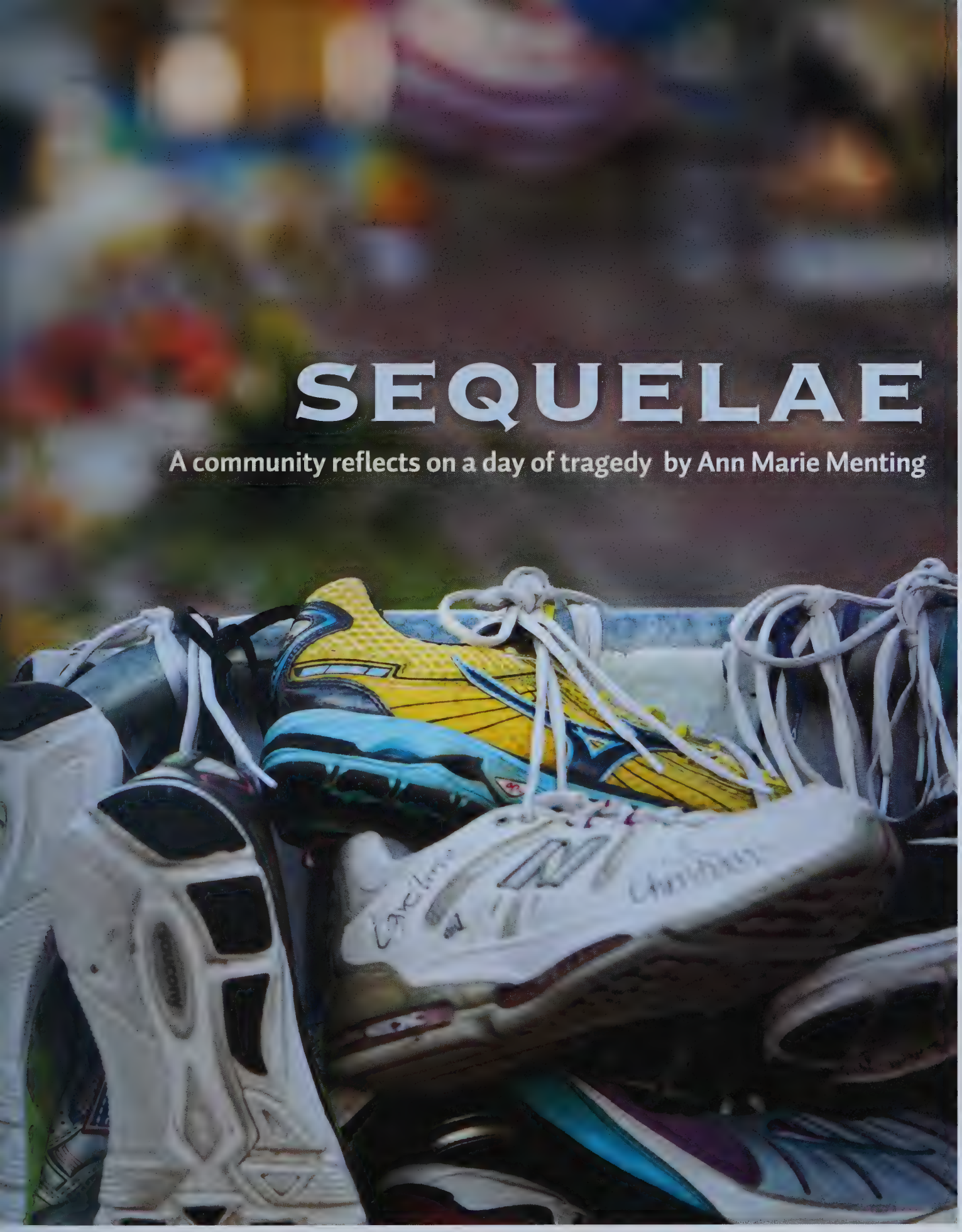
Fundamentally, Finland attempted to inculcate "rational" therapeutics—the right drug for the right patient at the right time at the right cost—more generally. In the 1950s, the U.S. Food and Drug Administration was still assessing only drug safety, not efficacy. Infuriated by combination antibiotic products promoted on the basis of what were largely testimonials, Finland argued for the importance of the controlled clinical study to underpin rational therapy. By 1959, his protestations were picked up by the popular press, just as Senator Estes Kefauver was about to begin his landmark investigations into the pharmaceutical industry. The Kefauver–Harris Amendment to rules governing the approval of new drugs had passed by 1962, mandating proof of drug efficacy via "adequate and well-controlled" studies by qualified investigators.

Today, the legacies of Waterhouse, Holmes, and Finland continue to shape the many approaches to infectious disease investigation at HMS. Whether devising and testing new vaccines, discovering novel targets for antimicrobials, monitoring or attempting to prevent antimicrobial resistance, or taking measures to ensure the rational worldwide delivery of antimicrobials to those who need them, HMS researchers continue to confront infectious disease at the intersection of patients and clinicians, bugs and drugs, and science and society. ■

Scott H. Podolsky '97 is director of the Center for the History of Medicine at the Francis A. Countway Library of Medicine and an associate professor in the School's Department of Global Health and Social Medicine.

SEQUELAE

A community reflects on a day of tragedy by Ann Marie Menting



ARAM BOGHASIAN; JOHN SOARES (PREVIOUS SPREAD)

Boots paced Boylston Street just hours after running shoes had slapped its surface on Patriots' Day 2013. The joy of the annual Boston Marathon had been violently displaced by feelings of disbelief and confusion that were shared by residents and visitors. On the HMS campus, however, those feelings were quickly submerged, replaced by a need to help, a drive to serve, and a compulsion to undo the damage done to those who had been maimed, injured, traumatized. HMS students and alumni recall the experiences of that day.

The Expectation

Anne Stack '88 turned to Twitter to confirm the news. "It was so out of context that I wondered if it could be real." Then she logged on to CNN. "Feed after feed was saying, 'Explosions at the finish line. Major injuries.' That was enough confirmation for me to know something bad had happened."

On April 15, Stack, anticipating traffic from marathon spectators, had arrived at work early and reported to the emergency department. It was 2:58 p.m., and the department's radio, the one linked to the Boston EMS, was reporting a crisis. "We initiated Code Triage, the hospital's disaster plan," says Stack, an HMS associate professor of pediatrics and clinical chief of the Division of Emergency Medicine at Boston Children's Hospital, "and we began to prepare for a potential mass casualty event."

Notified that they were about to receive "three criticals," Stack, who had been designated as trauma team leader, began to organize three trauma teams. At 3:15 p.m., the first patient, a seven-year-old girl, arrived. "I remember the medics' faces; they looked shaken," says Stack. "The first thing one said was, 'Tourniquet time, 1500 hours.' I didn't know what he was talking about. 'Tourniquet?' He didn't reply, just moved his eyes to where her left leg was. I picked up the sheet and knew then what he was talking about."

Stack's team swarmed around the girl, checking her airway and circulation, looking for injuries, providing her antibiotics, dressing her wounds. "She smelled like burned hair and soot and explosion," says Stack. "She was understandably dazed. We were asking her questions, but she couldn't hear well. The explosion had ruptured her eardrums." Then, in keeping with procedure, the team rolled the girl over to check her back.

"There were multiple shrapnel wounds," says Stack, "and there were nails and BBs. As I began to remove some of the superficially embedded material, I felt a moment of disgust. I could not believe someone would do this to inflict even more injury. That shook me for a moment, but I realized I needed to refocus to care for her."

Stack had worked in Haiti after the earthquake in 2010 and recalls that the emotional consequences of that deployment had surfaced a couple of weeks after she returned. Stack expected the same emotional response to the bombings, but it never came. "Here, the system worked beautifully," she explains. "I was proud of our team, proud of the hospital's response. Everyone rose to the top of their game; there was this feeling of overwhelming thankfulness."

The Response

"It wasn't silent," says Arun Ramappa '96. "There were a lot of different voices. There were a lot of players in this cast."

That cast included emergency medical technicians, physicians, residents, nurses, and a host of other caregivers who were either at Beth Israel Deaconess Medical Center or near enough to return when word of the blast began percolating through the hospital community.

AP PHOTO/ELISE AMENDOLA

Ramappa, an HMS assistant professor of orthopedic surgery and chief of sports medicine and shoulder surgery at the hospital, had been in his office completing some paperwork when his fiancée called him. She had tried repeatedly to reach him, Ramappa says, but "for some reason the phone wasn't working." Then a colleague who was on call for orthopedic trauma told him there had been a blast. "She headed for the emergency department, and I quickly followed," he says.

At the emergency department, Ramappa was tasked to triage patients to determine which victims needed to be sent to the operating room and in what order. He estimates that he assessed a number of patients that totaled "in the teens," and assisted in about seven surgeries.

"Patients were lined up side by side, so you'd have one set of caregivers assisting one patient and another set caring for the next, and the next, and the next. There were a lot of separate conversations going on." Despite the rapid influx of a large number of patients, says Ramappa, "we were able to handle things well. It was quite amazing, the response."

It's that response that has stayed with Ramappa. "That day showed how this community could come together. As we were working and working with patients, people showed up, all these caregivers eager and waiting to help."

AFTERMATH: The responsibility of caring for people injured in the marathon bombings first fell to those staffing the medical tent, set up near the race's finish line. The intense follow-up to the tragedy meant layers of police and security personnel guarding entrances to hospitals in the Longwood Medical Area, including those of Beth Israel Deaconess Medical Center, where one of the alleged bombers was later hospitalized.

GETTY IMAGES NEWS/JARED WICKERHAM

"Being able to help that day was gratifying and affirmed for me why I became a doctor," Ramappa adds. "For me, the lasting image of that day is all those people. There. Ready."

The Purpose

The text message on Brian Grottkau's mobile phone read, "We're okay, don't worry." It was from his wife, who Grottkau knew was at the marathon, cheering on her brother.

Grottkau '89 tapped a reply, "What are you talking about?" Her response prompted him to wrap up the preoperative discussion he was having with a patient and to head for the operating rooms where Grottkau, an HMS assistant professor of orthopedic surgery and chief of the pediatric orthopedic service at the Mass General Hospital for Children, was about to become, as he puts it, "a minor bit player in a real big production."

Together with R. Malcolm Smith, chief of the orthopedic trauma service at Massachusetts General Hospital, and a troop of residents, Grottkau began checking the operating rooms, dropping off residents as necessary to augment teams working with victims who were dazedly answering questions from doctors and police. At the final room, Grottkau became the attending on a traumatic amputation. Later, he triaged newly arrived victims.

But it wasn't until he arrived home that Grottkau felt the full weight of the day. "I was watching the bombing on the news and heard the disbelief in the voices of my wife and kids."

"I went to the Watertown Police Department a couple of days later and asked one officer, a friend, how he was doing. 'Were you involved in the shootout?' He told me he had been. 'Thank you,' I said. 'Did you care for some of the victims?' he asked me. I told him, 'I did a little.' 'No,' he said, 'thank you.'"

Reflecting on that conversation, Grottkau says, "You do your job and you do what you think is right. I just did my job. The reason I became a doctor was to help people."

The Bond

It was the first day of their family vacation. Edward Kenneth Rodriguez '97, his wife, and their three children had traveled to Southern California, where Rodriguez had attended graduate school. He planned to show them the highlights of the area, beginning with a meal at a favorite restaurant. He was about to tuck into a burrito when his wife, who was seated facing a television screen, put down her food. "She said, 'Oh my God! Look!'" Rodriguez recalls.

Rodriguez turned and saw the news flashes of the bombing in Boston. "My cell phone began to ring," he says. As an HMS assistant professor of orthopedic surgery and chief of orthopedics trauma surgery at Beth Israel Deaconess, Rodriguez is high on the emergency call phone tree. He started making calls to his team and learned there was a sufficient number of surgeons responding to the crisis. But his other questions would go unanswered; his phone calls would no longer go through.

Rodriguez took the next flight to Boston, a red-eye that landed around 5:00 a.m. "I went straight to work," he says.

On that morning after the bombing, Rodriguez began to handle the second round of debridements for some of the victims. Trauma care for amputations involves the immediate removal of debris and dead and damaged tissue, a wait of 24 hours, then successive surgical debridements until the wound is considered safe from infection, and safe to close. It's a procedure that has been honed on the battlefield. "Unfortunately," says Rodriguez, "in the past ten years or so, we've had a tremendous amount of information coming into the medical community via the military on how to handle blast injuries."

Rodriguez is no stranger to trauma injuries, having gone through fellowship training at the R. Adams Cowley Shock Trauma Center at the University of Maryland Medical Center. During his year there, which occurred early in the Iraq conflict, he helped care for overflow patients transferred from Walter Reed Army Hospital. And while he has worked with similarly injured victims of accidents or workplace explosions, "This was a group of young patients. And truly innocent," says Rodriguez. "These people had done nothing to bring this upon themselves. They had just planned to enjoy a beautiful day in Boston. I know we provided good care, and I'm proud of how well we worked together to help the patients. But I also think of how the world has changed for them."

The Future

The Patriots' Day holiday meant that many students tossed out their usual routines in order to get in some marathon watching, some gathering with friends, some extra study, or some welcome shuteye. This free-form scheduling presented a challenge to those responsible for accounting for the whereabouts of all University students following the bombings. For Nicholas Christakis '88, who is now the Sol Goldman Family Professor of Social and Natural Science at Yale University, and was then an HMS professor of medicine and co-Master of Harvard College's Pforzheimer House, that accounting meant gathering information on the nearly 400 students who live in the undergraduate residence. For David Roberts '95, an HMS associate professor of medicine and the director of the principal clinical experience at Beth Israel Deaconess, it meant handling a deluge of text messages from students eager, but uncertain whether, to help.

Two of those HMS students were Eduardo Hariton '14 and Nina Gold '14. April 15 found them on the cusp of their fourth year—and of an experience that would confirm for them the wisdom of their career choices.

Hariton was at home when news of the bombings came. "I paged my chief resident from the trauma service and said, 'If you need an extra body, I'm happy to come in.'" The uncharacteristic reply came within minutes, "This one time you should come in." Hariton tossed on some scrubs and ran the few blocks to Beth Israel Deaconess.

As he ran, Hariton had disjointed thoughts of lessons learned in Israel during his work as a first responder for that nation's emergency medical service, Magen David Adom: apply tourniquets on severed limbs to control bleeding; shrapnel will increase the number of injured; if the bomb was big, victims will have significant burns.

At the emergency department, he was directed to find a room with a patient and to stay with that patient; he was to provide continuity as caregivers came and went. Hariton stayed with two victims; each had fractures and wounds embedded with shrapnel.

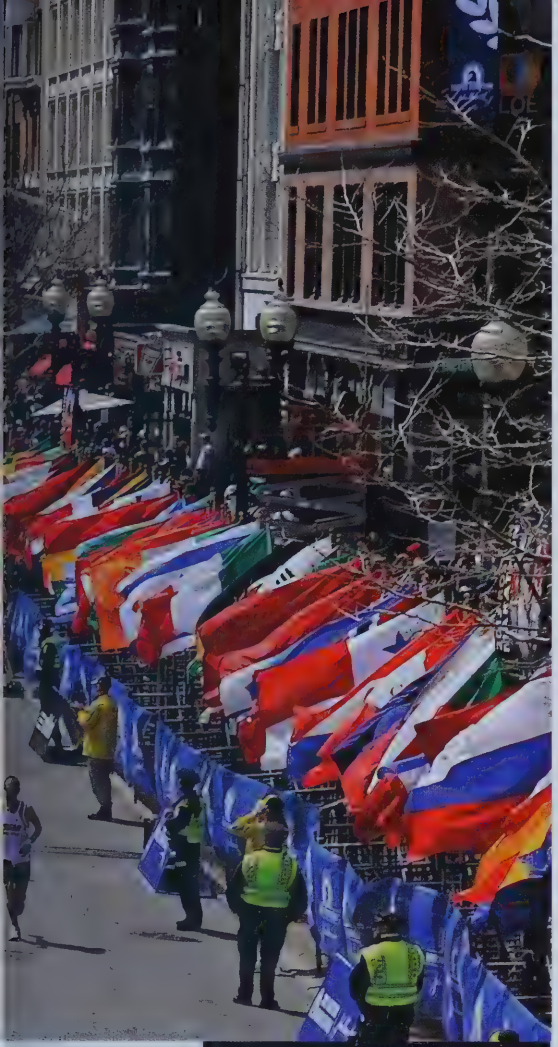
By early evening, things had quieted. "The adrenaline stopped pumping, and I started reflecting," says Hariton. "I had a sense of fulfillment. I hadn't taken care of severely injured people, but I had watched the people I had trained under for the past three months do so and knew that one day I would be able to give that sort of care. I was proud to be part of that team."

Gold's role in caring for the injured came in the days following the bombings. As a medical student with the consult liaison psychiatry team at Beth Israel Deaconess, Gold was a part of the team's efforts to help victims cope with the trauma they had experienced.

Relaxation exercises were key to that end. Getting victims to relax to the point where they choose to speak about their experiences, rather than being pressured to talk about them, has been shown to be helpful for victims and their families. Gold recalls seeing how effective this approach can be. "I watched a senior psychiatrist work with a patient. He began by simply asking the patient to relax every muscle in his body, from his face down to his toes. As he did this, I saw peace come over the man's face." Learning to self-soothe, says Gold, can be especially vital to those with amputations who begin to experience neuropathic pain.

Working with the team, Gold was "uplifted by the resilience I saw in the patients. Yet I still feel horrified by this act of violence. I'm upset that the city I grew up in was victimized."

GETTY IMAGES/BOSTON GLOBE



BEFORE THE STORM: A view of Boylston Street as marathon runners approached the finish line shortly before the two blasts.

But as far as her chosen field, Gold is more certain than ever it's right for her. "I am proud to be a part of the medical community. It's the only thing I can imagine myself doing."

The Insight

Joaquim Havens '04 was deep into a discussion of data with a hospital resident when he heard a knock on his office door. "It was a frantic knock," says Havens, "and when we answered, the request was urgent. 'They need you in the emergency department right now.'" So Havens, an HMS instructor in surgery at Brigham and Women's Hospital, headed for the emergency department. There, he pushed open the double doors and looked upon a scene of "controlled chaos." He approached the first senior staff person he saw: "What can I do to help?"

Asked to evaluate the patients, Havens began going room to room, checking each patient's breathing and blood pressure and ensuring there were resources available for the patient's needs. When it was determined that sufficient resources had been deployed and the situation was under control, Havens and others began to prepare for the next wave of patients.

"Ultimately, we treated 39 casualties," says Havens. "Twenty-three arrived in the first hour." The patients ranged in age from 19 to 65.

Eleven patients underwent surgery that first night; Havens performed one of the surgeries, handling a penetrating wound to the neck.

As associate director of the hospital's surgical residency program, Havens was pleased at the residents' response to the crisis. "We had nearly every surgical resident in training there and helping," he says. As valuable as that experience was to the residents, it has led to some emotional ups and downs. "We've done some deep reflective briefings on coping with this experience, both emotionally and medically," adds Havens. The talking also helped him. "I opened up about myself, too, and shared my fears and feelings and emotions. I'm an attending, but I wanted them to realize that this sort of experience affects me as well."

Those conversations, and a weekend with his wife in Maine, have helped Havens get back to normal. For him, that has meant "not watching the news and not thinking about that day each waking moment. It has meant trying to feel like the world hasn't completely changed."

"Being a doctor is a lot more than amassing a volume of technical knowledge," Haven adds. "It's interacting with patients, their families, your colleagues, and the people you're training. You can't separate yourself from this work. You take a little piece of it home with you every day."

The Unexpected

Glenn LaMuraglia '79 walked along Boylston Street the day before the marathon. He lives blocks from the finish line, so this was a neighborhood amble. "It was a sunny day," says LaMuraglia, "and there were all these happy people walking along, speaking so many different languages, and wearing the blue and yellow shirts of the Boston Athletic Association. I remember thinking, 'Wouldn't it be nice next year to maybe work out and run the marathon?'"

That warm mood dissolved the next day when LaMuraglia, an HMS associate professor of surgery at Mass General, was closing after surgery on an aneurysm. A nurse had entered the operating room to ask the scrub nurse to stay around. "We asked, 'What's going on?'" says LaMuraglia. He and his colleagues then learned of the bombings.

The surgical team finished its work, and LaMuraglia set out for the hospital's emergency department. "When I arrived, it was obvious the place had been filled with people who had been bleeding," he says. "There were sheets and dressing wrappers and other stuff all around. And there was blood on the floors of various cubicles." As LaMuraglia walked by one room, he saw a patient inside. He asked the physician in the room, George Velmahos, the HMS John Francis Burke Professor of Surgery at Mass General, if he could help.

"'Well, Glenn,' he said, 'I'm glad you came by. We've had a series of patients come in with their legs blown off. But this is one we may be able to save.'"

LaMuraglia joined the effort. The team fixed the fracture using an external structure of pins and wires, and LaMuraglia worked to re-establish a blood supply to the limb. "Everyone rose to the occasion," he says, "the nurses, the techs, the operating room staff all were phenomenal. Things appeared as if by magic."

"We all were so focused," adds LaMuraglia, "just concentrating on the work. We ended up taking a two- or three-inch piece of metal out of the patient's leg; I think it was a piece of a pressure cooker."

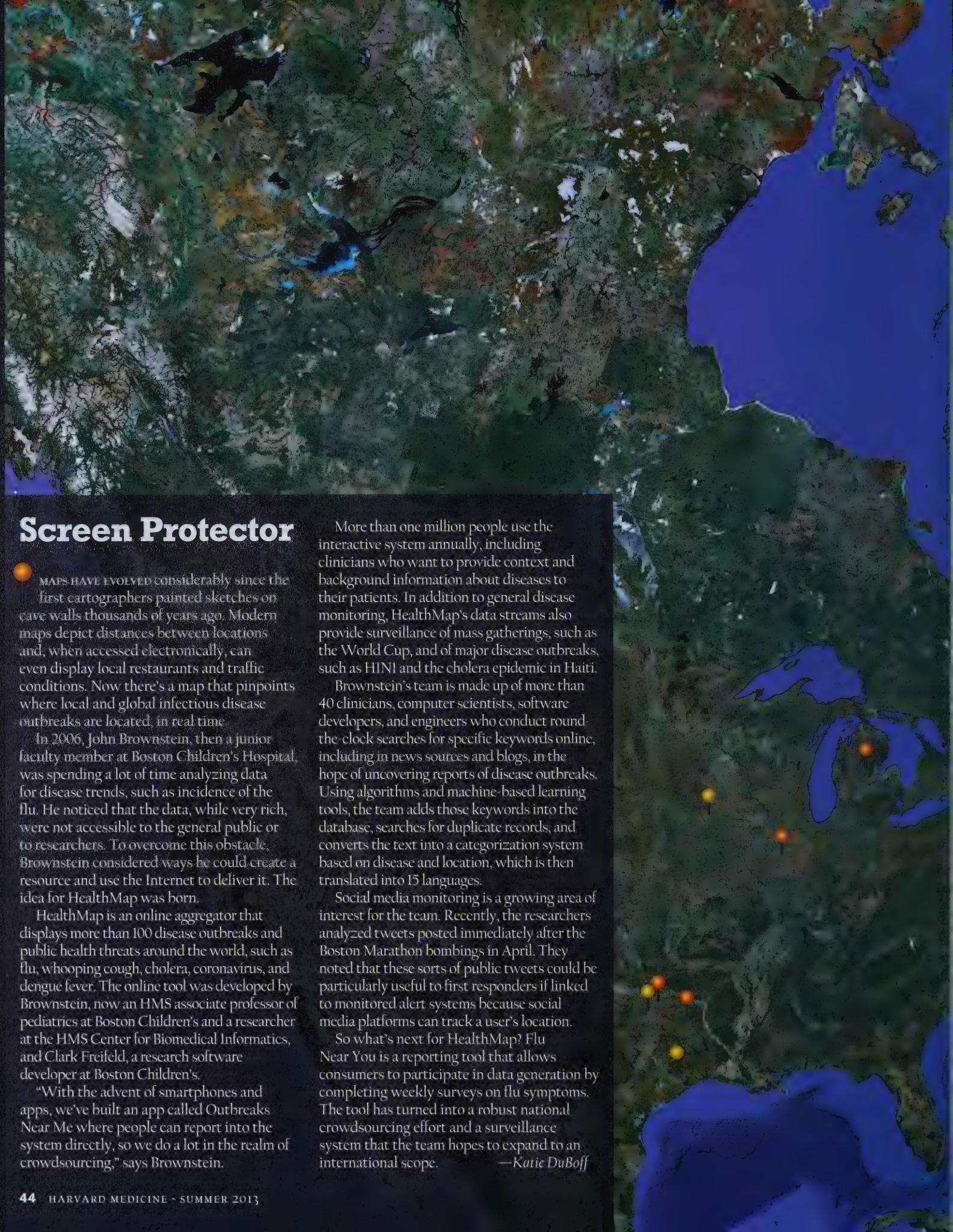
The structure securing the fractured bones needed to be readjusted under x-ray, so, before LaMuraglia could continue, he had to step out of the operating room.

In that moment of stillness, something happened to LaMuraglia, something "that's never happened to me in all my years as a surgeon." His eyes welled up. "For all the surgeries I've done and the patients I've cared for, this one tasted different. This one had a flavor that was tragic."

The operation continued, and LaMuraglia performed a venous bypass linking the blood supply from behind the knee to the ankle. To the joy of the team, the foot began to pink. That elation, however, was shattered a couple of days later. The damage to the limb had been so extensive that the orthopedic team determined it was better to remove it.

A week or two later, after Boylston Street had been reopened to pedestrians, LaMuraglia again took a morning walk. Visiting the makeshift memorial that had become a site of public grief and condolence, LaMuraglia noticed that one of the barriers that formed the memorial's backbone had toppled over. So, together with a kid who was standing nearby, LaMuraglia righted the structure. "We were able to get it back to normal," he says. ■

Ann Marie Menting is editor of Harvard Medicine *magazine.*



Screen Protector

MAPS HAVE EVOLVED considerably since the first cartographers painted sketches on cave walls thousands of years ago. Modern maps depict distances between locations and, when accessed electronically, can even display local restaurants and traffic conditions. Now there's a map that pinpoints where local and global infectious disease outbreaks are located, in real time.

In 2006, John Brownstein, then a junior faculty member at Boston Children's Hospital, was spending a lot of time analyzing data for disease trends, such as incidence of the flu. He noticed that the data, while very rich, were not accessible to the general public or to researchers. To overcome this obstacle, Brownstein considered ways he could create a resource and use the Internet to deliver it. The idea for HealthMap was born.

HealthMap is an online aggregator that displays more than 100 disease outbreaks and public health threats around the world, such as flu, whooping cough, cholera, coronavirus, and dengue fever. The online tool was developed by Brownstein, now an HMS associate professor of pediatrics at Boston Children's and a researcher at the HMS Center for Biomedical Informatics, and Clark Freifeld, a research software developer at Boston Children's.

"With the advent of smartphones and apps, we've built an app called Outbreaks Near Me where people can report into the system directly, so we do a lot in the realm of crowdsourcing," says Brownstein.

More than one million people use the interactive system annually, including clinicians who want to provide context and background information about diseases to their patients. In addition to general disease monitoring, HealthMap's data streams also provide surveillance of mass gatherings, such as the World Cup, and of major disease outbreaks, such as H1N1 and the cholera epidemic in Haiti.

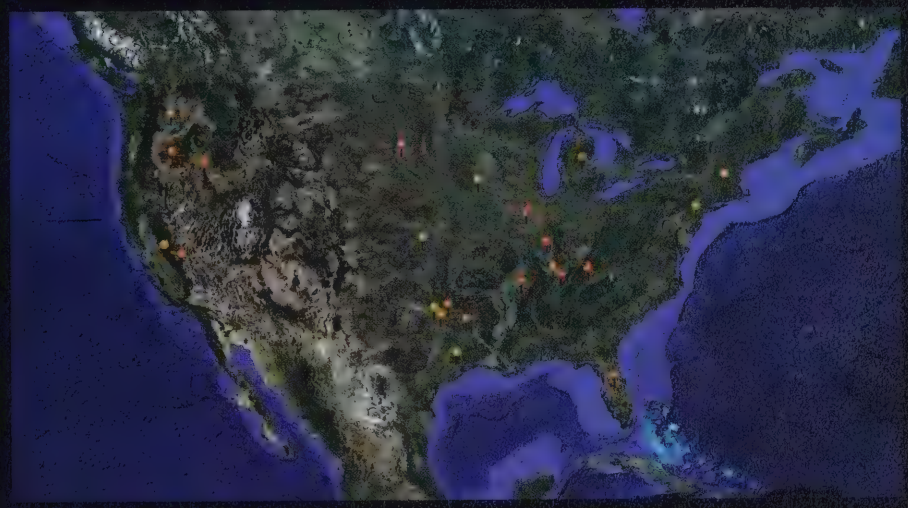
Brownstein's team is made up of more than 40 clinicians, computer scientists, software developers, and engineers who conduct round-the-clock searches for specific keywords online, including in news sources and blogs, in the hope of uncovering reports of disease outbreaks. Using algorithms and machine-based learning tools, the team adds those keywords into the database, searches for duplicate records, and converts the text into a categorization system based on disease and location, which is then translated into 15 languages.

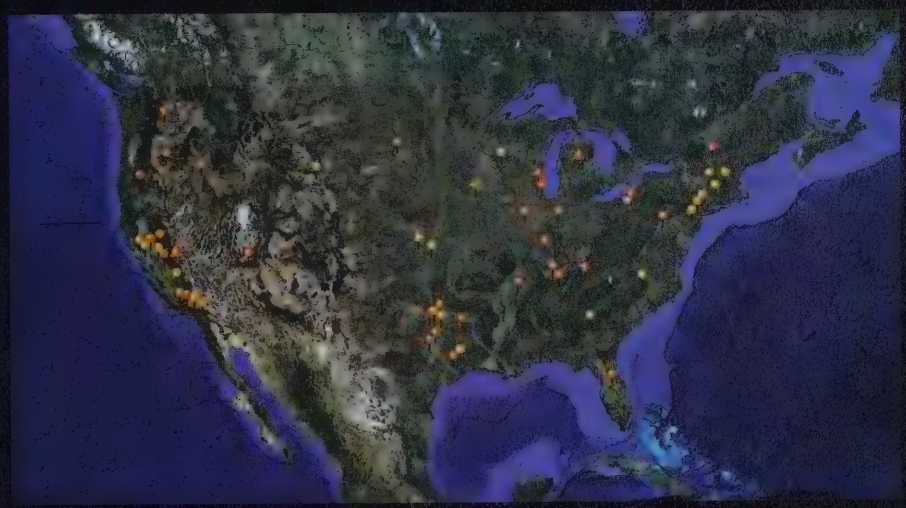
Social media monitoring is a growing area of interest for the team. Recently, the researchers analyzed tweets posted immediately after the Boston Marathon bombings in April. They noted that these sorts of public tweets could be particularly useful to first responders if linked to monitored alert systems because social media platforms can track a user's location.

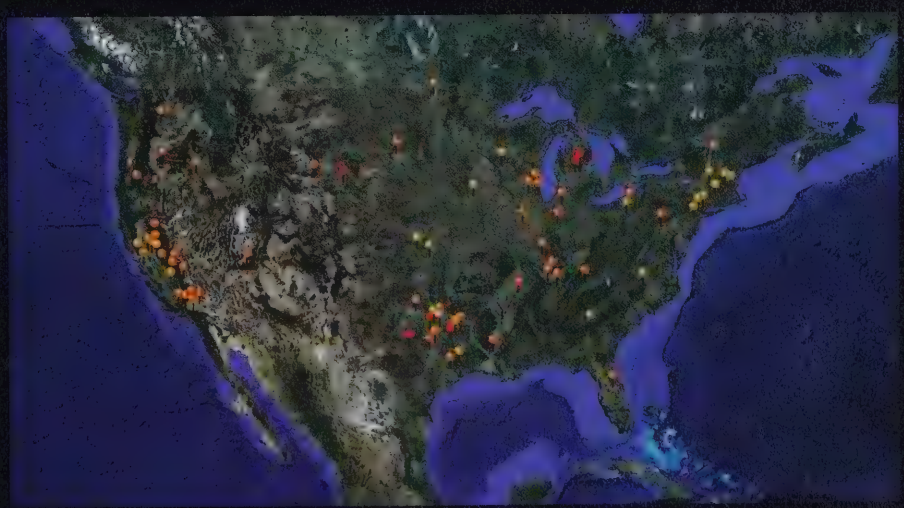
So what's next for HealthMap? Flu Near You is a reporting tool that allows consumers to participate in data generation by completing weekly surveys on flu symptoms. The tool has turned into a robust national crowdsourcing effort and a surveillance system that the team hopes to expand to an international scope. —*Katie DuBoff*

SMART SCIENCE

THE FUTURE OF MEDICINE IS NOW







VIEW POINTS: These satellite images show the reported incidence of West Nile virus, as compiled by HealthMap scientists. The page at left shows incidence on June 21, 2013. To the right is shown the aggregated incidence over the previous five days (top), the previous two weeks, and the previous one month. The different colors of the pins indicate the severity of the outbreak, ranging from yellow (lowest) to red.

MATTIAS PALUDIHEALTHMAP

BACKSTORY

FROM THE COLLECTIONS AT HARVARD MEDICAL SCHOOL

Head lice. The mere mention triggers an itch response. *Pediculus capitis* and its close relative, pubic lice, *Pthirus pubis*, are human-specific parasites, and have lived with us for thousands of years. They cannot survive anywhere but in human hair and cannot eat anything other than human blood. Body, or clothing, lice are a different species, and are known vectors for several human diseases, including louse-borne typhus fever.

Hans Zinsser, an HMS professor of bacteriology and immunology from 1923 until his death in 1940, authored *Rats, Lice and History*, a biography of typhus. Although Zinsser's thesis that the head louse was a vector for typhus was later disproved, his research on insect vectors advanced the understanding of human infectious disease.

But even the lowly louse does some good in the world. Researchers are studying the divergent evolution of head and body lice to determine when humans shed most of their body hair and began wearing clothing. Losing body hair allowed early humans to sweat more efficiently, useful when running distances to hunt food, and the protection provided by clothing allowed migration out of Africa into cooler climes.

—*Susan Karcz*

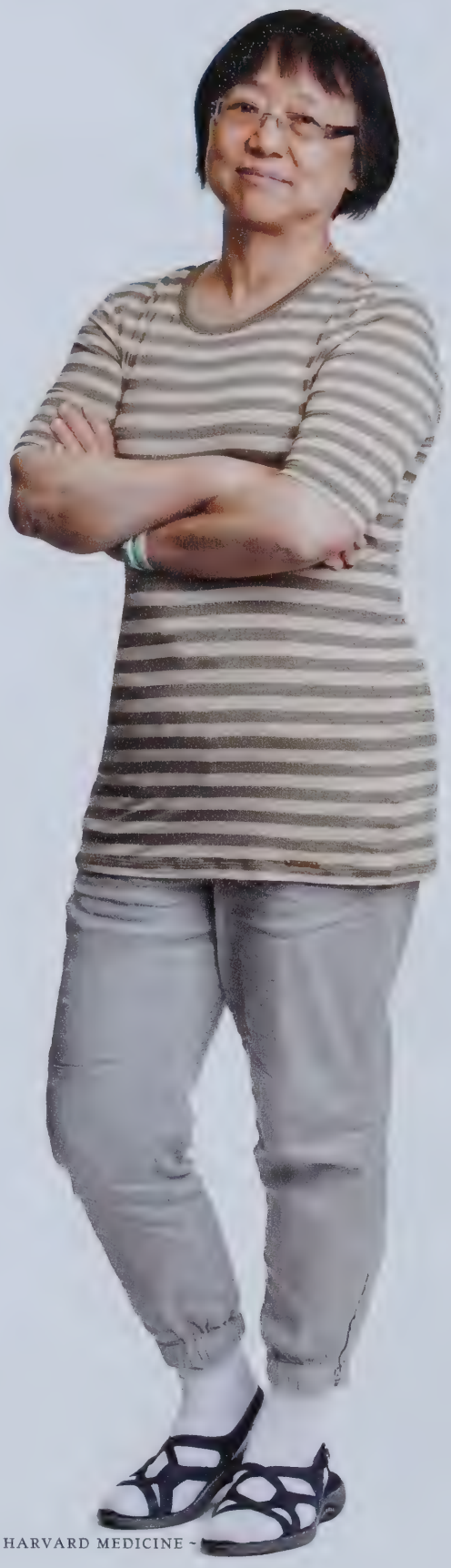
PAUL WURTZMAN

ALL LOUSED UP: Objects include, clockwise, from left, a World War II-era military-issue rotary insecticide applicator used to delouse soldiers' clothing; a series of brass clamps that immobilized lice as glass capillaries were used to anally infuse epidemic *Rickettsia prowazekii* for vaccine research and development, circa 1930s-1940s; the insignia of the Noble Order of the Golden Louse, created in 1915 by Frederick Cheever Shattuck, Class of 1873, and awarded for service in combating typhus in Serbia in 1916; models of the nervous systems, the target of most insecticides, of (from top) a butterfly, a chrysalis, and a caterpillar, made by Louis Thomas Jérôme Auzoux, a French anatomist and naturalist, circa 1851; and a cuff containing a mesh-covered louse container, circa 1970s. When the cuff was strapped to the arm of a researcher, lice placed in the container could partake of a blood meal.

Brass louse holder, insecticide applicator, and cuff with mesh container courtesy of Richard Pollack, an instructor at the Harvard School of Public Health. Auzoux model courtesy of the Warren Anatomical Museum at the Countway Library of Medicine. Order of the Golden Louse award courtesy of the Boston Medical Library at the Countway Library.

FIVE QUESTIONS

FOR JUNYING YUAN



Professor of Cell Biology, Harvard Medical School

Did you always hope to have a career as a scientist?
At one time I had no idea that I would even go to college. I grew up in China during the Cultural Revolution, when most colleges were closed for more than ten years.

I had a high-school teacher who believed I should go to college. But the middle-school education I had received had not prepared me for the exams. What was worse, I had no textbooks for study. My high-school teacher helped me; he stole textbooks from the library so that I could study. I did and scored number one in Shanghai. This ranking earned me the opportunity to attend Fudan University in Shanghai.

What inspired you to study regulated cell death?
During my second year of graduate school at HMS, I took a class about neurodegenerative disease and became curious about how a cell dies. I learned that these diseases are caused by the death of specific neurons, not by a total loss of neurons. I wondered how one population of neurons could be affected while others remained mostly okay. Since selectivity in biology means regulation, I thought that cell death must also be regulated. But most people in the field then were interested in studying suppression of cell death, not about how cells die. I decided I wanted to study cell death.

How did you manage to do research at MIT when you were a student at Harvard?
It was hard to find a faculty mentor who was researching cell death. By chance I attended a seminar by H. Robert Horvitz from MIT on programmed cell death in the nematode *Caenorhabditis elegans*. Most people paid little attention to *C. elegans* at the time: How can a little worm be relevant to humans? But it was the only model I could use to study cell death, so I joined Horvitz's lab.

Has this research taken you in unexpected directions?
Yes. I'm now investigating necrosis, a common aspect of human disease that many have considered to be passive cell death and, therefore, unregulated. We observed a form of necrosis that was regulated and discovered a molecule with drug-like properties that targets the enzyme involved in that regulation. This discovery has led to studies of the mechanism of necrosis and its role in human disease.

What compels you to question the dogmas about processes such as regulated cell death and necrosis?
As a scientist, you must dig deeply. It's difficult to remain confident when you're working in an area that most consider well defined, but that *you* think remains unknown. You ask: Is my hypothesis correct? But no matter what, you must go ahead and test it. You must have confidence in yourself.

—Elizabeth Dougherty

JOHN SOARES

President's Report

Welcome, Class of 2013, to the community of HMS alumni, linked by the shared experience of starting our journeys as physicians at HMS. The welfare of today's HMS students is an enduring concern of the Alumni Council, your elected representatives. Three times each year, we meet with everyone from the Dean to current students to monitor the School's activities and to seek ways to engage alumni in them.

At our spring meeting, we heard about the ongoing review of the preclinical curriculum and about renovations to the Tosteson Medical Education Center. The curriculum review may bring changes to the design of the first two years of study.

The Council has been collaborating with the Center for Primary Care, which offers HMS a new opportunity for alumni involvement. We are exploring opportunities that would link alumni with HMS students interested in careers in primary care.

It's been my honor to have served as Alumni Council president, and I salute my successor, Laurie Green '76.

Nancy Rigotti '78 is an HMS professor of medicine at Massachusetts General Hospital.

STANLEY ROWIN; CHANNING JOHNSON (FAR RIGHT)

FAMILY AFFAIR: Bobby Murray (left), widow of Joseph Murray, and daughter Katherine attended the transplantation symposium

MURRAY'S HEIRS

Progress in transplantation and organ regeneration shared with alumni

Fifty-eight years after Joseph Murray '43 performed the first successful human organ transplant, a faculty symposium dedicated to his memory featured four pioneers who are striving to restore organs and even faces lost to disease or trauma.

The challenge Murray met in 1954 still confronts medicine: How can the body accept foreign tissue as its own? Murray, who won the 1990 Nobel Prize in Physiology or Medicine, developed the first immunosuppressive drugs, extending transplantation beyond identical twins.

Tissue rejection remains a hurdle. Patients must take powerful drugs for a lifetime and risk increased vulnerability to cancer and infection because their immune response has been muted.

Tolerance—a state in which tissue donated by an unrelated person or engineered in a lab does not provoke rejection—is still the holy grail, speakers told an audience in the Joseph B. Martin Conference Center. That audience included Murray's widow, Bobby, and two of their six children: Katherine Murray-Leisure '78 and Richard.

Terry Strom, an HMS professor of medicine and codirector of the Beth Israel Deaconess Transplant Institute, hopes to create tolerance by tilting the balance between immune cells that aggressively attack a transplanted kidney and immune cells that protect that new organ as "self." Experiments in animals have induced tolerance by exposing the recipient to antigens from the donor before transplantation.

"Our hope is to liberate patients from the immunosuppressive agents they must take," he said.

Joseph Vacanti, the HMS John Homans Professor of Surgery and chief of pediatric surgery at Massachusetts General Hospital, wants to alleviate the shortage of organs available for transplant by building them. Working with tissue engineering scientists from MIT, he also hopes to eliminate rejection by using cells that create their own tissue on synthetic scaffolds.

A. Benedict Cosimi, the HMS Claude E. Welch Distinguished Professor of Surgery and chief emeritus of the Division of Transplantation at Mass General, is researching donor-specific tolerance. Called chimerism, the technique introduces a donor's bone marrow cells into a recipient before transplantation.

Bohdan Pomahac, an HMS associate professor of surgery and director of plastic surgery and transplantation at Brigham and Women's Hospital, shared lessons learned from five of his patients—Jim, Dallas, Mitch, Charla, and Carmen—who now have new faces and new lives.

He said immunosuppression is a challenge in the complex feat of face transplantation. Because patients can live without face transplants, the decision to take the drugs comes down to quality of life.

Pomahac showed before-and-after photos of this patients, to gasps from the audience. Then he showed one more.

"Dallas got married this past spring," he said.

—*Elizabeth Cooney*

JOHN SOARES

THE ART OF FORGIVING

HMS alumnus finds poetry in medicine and the human condition

When a gravely ill patient asked him for forgiveness for not responding to the treatment he had administered, Rafael Campo '91, HMS associate professor of medicine at Beth Israel Deaconess Medical Center, was at first astonished. Then Campo became haunted by the irony of his patient's words. "Throughout the course of his illness, I had acutely felt the limitations of the biomedical model and my own personal helplessness," Campo says. "I held myself responsible for his death, but didn't know how I could express my own wish to be forgiven."

Campo found a way to ask for that forgiveness in the poem "Morbidity and Mortality Rounds," winner of the 2013 Hippocrates Prize for Poetry and Medicine. The Hippocrates Prize, one of the most valued international poetry prizes, recognizes unpublished poems that address a medical topic. Campo's poem won first place in the Open International category, the top category among the several that make up the competition.

"I am delighted to receive this prestigious international prize," he says. "Through my poem, I hope I was able to address the power of empathy to combat the distance we almost reflexively adopt toward our patients and to confront some of our own shortcomings."

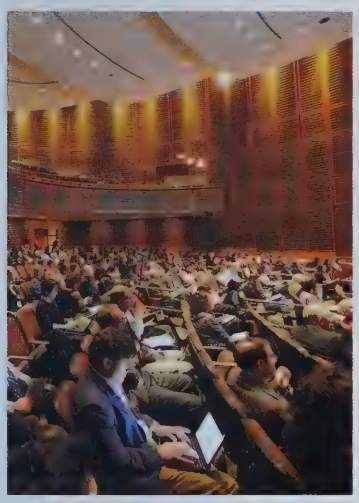
Campo accepted his award at the International Symposium on Poetry and Medicine in London on May 18. "Rafael Campo eloquently shows the power of poetry to help both health professionals and patients engage with and learn from each other under the most testing of medical and personal challenges," says Donald Singer, Hippocrates Prize cofounder and president of the Fellowship of Postgraduate Medicine, the major patron of the Hippocrates Initiative.

Campo's sixth collection of poems, *Alternative Medicine*, will be published later this year. His work is well known for addressing themes relating to humanism in medical practice. "Poetry, arts, and humanities in general are indispensable to the work of healing, in helping us to make sense of the human experience of suffering," Campo says. "Hospitals are full of humbling and indelible stories, and we can provide better care for our patients if we learn how to hear them."

In addition to his work as a teacher and a practitioner of general internal medicine, Campo serves on the faculty of the Master of Fine Arts creative writing program at Lesley University in Cambridge, Massachusetts.

Longwood Seminars Online

EACH SPRING, HMS SPONSORS the Longwood Seminars, a "mini-med school" public lecture series. Presented by School faculty, this year's seminars covered such popular topics as neuroengineering, dietary supplements, sleep dynamics, and the connection between belief and health. Links to videos of the lectures and to supplemental readings are available at http://hms.harvard.edu/news/longwood-seminars.



TAKING NOTES: Psychiatrists Erich Lindemann (center right) and Lydia M. Gibson Dawes (center left) at an unidentified social event. From the Lydia M. Gibson Dawes papers

The Private Side of Public Health

Collections at the Countway accessible for the first time

CONTEMPORARY DEBATES in the field of public health, those that range from the role of universal health insurance to the discourse around fundamental human rights and global health, are products of the times in which they arise. To be understood, they must be explained within their respective historical contexts.

In April of this year, the Center for the History of Medicine at the Francis A. Countway Library of Medicine, together with the Alan Mason Chesney Medical Archives of The Johns Hopkins Medical Institutions, began a project aimed at opening currently inaccessible public health collections to researchers to allow for just such historical research. The two institutions will concurrently develop best practices that will ensure that the information in the collections will remain protected. The project, Private Practices, Public Health: Privacy-Aware Processing to Maximize Access to Health Collections, will continue through April 2014.

The project will open the collections of seven leaders in the field of public health. Those being processed by the Countway include the professional papers of Stephen Lagakos, known for his AIDS research and work linking poor water conditions to public health problems; Erich Lindemann, a specialist in social and disaster psychiatry and community mental health; and Arnold Relman, an HMS professor of medicine emeritus and a former editor of the *New England Journal of Medicine* who has written on the economic, ethical, legal, and social aspects of health care.

As part of the project, the center and Hopkins will also address the need of the special collections community for best practices to process and describe collections containing restricted records. Whether privacy is legally mandated (as with HIPAA and FERPA), imposed by parent organizations (as governed by an institutional records schedule), or applied per local practice, all repositories maintain records that pose significant challenges to access.

The project has created a publicly accessible wiki that will carry information on project documentation, bibliographies, calls for participants in project activities, and information about upcoming events: https://wiki.med.harvard.edu/Countway/ArchivalCollaboratives/PrivatePractices.

CLASS NOTES

NEWS FROM ALUMNI

1943

Robert Jones

My second career of retirement has now been almost as lengthy as my medical practice—but less stressful. I lost my wife, Betty, to an obscure neurological disease (progressive supranuclear palsy) in 1999. Since then my son and I have traveled fairly extensively in Europe and China. I gave up tennis two years ago for the Silver Sneakers program. I live with my daughter, who is a family practitioner.

1947

Harold Braun

I am plugging along with age-appropriate logging, gardening, and writing about medical history. A recent Osler Society paper dealt with a patient I shared with Osler—a sure sign of aging.

1948

David Gibson

I'm pushing 90 and living in my hometown of Mansfield, Ohio, after spending 40 years as chair of the Department of Biochemistry and Molecular Biology at Indiana University School of Medicine.

1949 65th REUNION

Francis Riley

After my wife, Marion, died in 2011, I moved from Martha's Vineyard to Scottsdale, Arizona, next door to my son, Kenneth. I live alone in what is called a luxury retirement community, and enjoy it only to the extent that it allows me to be near my son.

1954 60th REUNION

Billy Collum

In July 2012, after 57 years as a physician, I fully retired from family practice. I have successfully adjusted. My progeny of eight are doing well and are happily married and working. Best regards to HMS!

Emanuel Rubin

I was recently funded as a principal investigator on a new five-year grant relating to the intrinsic (mitochondrial) pathway of programmed cell death. The 7th edition of *Rubin's Pathology*, which has now been translated into nine languages, will soon be published.

1955

William Bolman

I was appointed president of the Autism Society of Hawaii. Are any classmates involved in the expanding field of autism research?

1956

Richard Sogg

I'm still making music. I organized a tribute to Verdi and Wagner for the 200th birthdays of both in June. The tribute included a chamber performance of Wagner's *Siegfried Idyll*.

1957

Wilbert Aronow

The 5th edition of Tresch and Aronow's *Cardiovascular Disease in the Elderly* will be published by CRC Press in August.

JOHN SOARES

William B. Greenough III

I am a full-time member of the faculty at Johns Hopkins University School of Medicine and Bloomberg School of Public Health. Recent awards include the Mary Betty Stevens Award for Clinical Research given by the Maryland Chapter of the American College of Physicians.

Victor Sidel

Upon my retirement in January, I was named Distinguished University Professor of Social Medicine Emeritus at Albert Einstein College of Medicine and Montefiore Medical Center, and continue as an adjunct professor of public health at Weill Cornell Medical College. The 2nd edition of *Social Injustice and Public Health*, which I coedited, will be published this fall.

1959 55th REUNION

Kilmer McCully

My scientific and medical memoir was published this year by Nova Science. *Pioneer of the Homocysteine Theory* describes my origins, my education at Harvard College and HMS, my discovery of the homocysteine theory, and the development of a new strategy for the prevention and treatment of diseases of aging.

1960

Arthur Bank

My new book, *Searching for the*

Best Medicine: The Life and Times of a Doctor and Patient, has recently been published. It's part memoir, part medicine, featuring my views on medicine today and on changes in medicine and our society over the past 60 years.

Peter Barrett

I continue to enjoy my involvement in geriatrics at Harbor-UCLA Medical Center. I recently had a pleasant visit in San Francisco with **Rex Jamison**, and his wife, Dede—both are doing well. Last summer I spent a week cycling in the west of Ireland, and found that it consists primarily of rocks, sheep, and pubs. Great trip!

1961

William Ellis

A recent *Wall Street Journal* opinion piece on accountable care organizations, coauthored by the dean of HMS, did not mention tort reform. During my career as a full-time internist, I experienced one inappropriate lawsuit, which tort reform may have negated.

1963

James Cassady

I was recently awarded the American Society of Radiation Oncology Gold Medal for lifetime services and accomplishments.

David Sachar

My retirement in September from Mount Sinai hasn't kept me from my favorite academic medical pursuits, but it has afforded me more time for fun and frolic—including an amazing trip to Myanmar in November.

1965

John Mills

My daughter, **Christina '08**, her husband, and her son, Alexander, recently visited me in Melbourne. The weather mostly behaved itself by providing us with sunshine.

1966

Edward Goetzl

I am one of the recipients of the 2013 Dickson Emeritus Professorship Award for my work in cellular membrane vesicle diagnostics in neurodegenerative diseases. This award is given annually by the University of California San Francisco Office of Academic Affairs and Faculty Development and Advancement. It is most especially a tribute to all the high quality research collaborations I've had with so many talented scientists over several decades.

1967

Gerald Rogeli

I retired last June, but I'm busier than ever! I have been doing a locum tenens job in Bangor, Maine, since January. My wife, Diane, and all six grandkids are doing great!

1971

Judith Brice

My life has veered from medicine and taken some unexpected twists and turns. On the downside, after many months of severe hip pain in the same hip that was replaced nine years ago, I was fortunate to find a doctor who could identify the problem. Surgery, early in February, has brought great relief, but now I'm working on getting stronger. It doesn't come easy at 68! On the upside, I continue to derive great joy from my poetry. *Renditions in a Palette* should be appearing this fall. I think you will be surprised

JOHN SOARES

CLASS NOTES

NEWS FROM ALUMNI

to find where my thinking has gone these past 30-odd years, and as for me, I would love to hear your reactions and thoughts. Cheers to all. I cherish the memories of being with all of you.

Joel Greenberger

I have been inducted as a Fellow in the American College of Radiology. The induction ceremony was held during the organization's recent annual meeting in Washington, DC.

1972

Kim Masters

I am practicing as a child psychiatrist and medical director of a 58-bed child and adolescent psychiatric residential treatment facility. I teach physician-assistant students from two medical schools during their monthly clinical psychiatry rotations. I continue to have dreams of having to complete or redo medical school courses in order to graduate from HMS. I guess I absorbed the School's messages to us that "whatever treatments we are using today will need to change tomorrow," and "the best practice is the relentless search for answers no matter how satisfying our current opinion."

1974 40th REUNION

Thomas Najarian

Thanks to all who send in personal notes for our class. I've enjoyed reading what others in our class have been up to. After surviving several serious medical scares throughout the past 15 years, I figured I'd better write before the next note about me was an obit. My wife, Sue Unkel, and I have been retired from the active practice of medicine for several years. She is now free to serve as my full-time personal psychiatrist. I work part-time on medically related patents and inventions and am a part-time consultant to Vivus Pharmaceuticals, Inc. We hope to see many of my classmates next summer at HMS. We are living in Lake Tahoe and would welcome visitors to this area to stop by and say hello.

Edmond Raker

I'm still enjoying family, teaching surgical residents, and practicing vascular surgery. Best to all classmates!

1978

Mariette Murphy

I'm reaping the rewards of my 24-year practice at Mass General. My second generation of pediatric patients who have "graduated" are bringing their children to me as are my adolescent program patients. And I am enjoying my one-year-old grandson, Dermot, my daughter, Marisa, and her husband, Joe.

1979 35th REUNION

Richard Rowe

Running in the Boston Marathon and seeing the excellent response of the medical community was an incomparable experience. I salute the Boston-area hospitals and citizens for their impressive response and ongoing help in the recovery of the injured.

1981

Ignacio Magana

I am now in academic practice in Ethiopia. I use the name Tony because the people here find that easier to pronounce.

1982

Beth Karlan

I was appointed by President Obama to the National Cancer Advisory Board.

JOHN SOARES

1983

Christopher Coley
My son Alex finished his first year at UC Berkeley School of Law in May. He will spend the summer in Tokyo as an associate with a San Francisco-based law firm.

1986

Eric Bing
I have been appointed professor of global health at Southern Methodist University. Since 2011 I have been a senior fellow and director of global health at the George W. Bush Institute at SMU.

1993

Phuong Nguyen
I recently completed my 21st Operation Smile mission as an anesthesiologist. Since 2005, I personally have helped bring 444 new smiles to children with cleft lips and palates.

1995

Felix Nunez and Chasity Jennings-Nunez
Our family is doing well. Chasity is thriving in her practice here in Los Angeles, and Felix is working hard as chief medical officer at a community health center.

2003

Lawrence Gulotta
I am an assistant attending orthopedic surgeon at the Hospital for Special Surgery. My wife and I have moved to Chappaqua, New York, with our three sons.

2006

David Hwang and Janice Jin Hwang
We welcomed a new baby girl, Julia Chun-Xi, into our home in Guilford, Connecticut, on March 26. Her two-year-old big brother, Theo, is very excited!

2007

Cindy Lin
I relocated to Singapore with my husband, James Lee, after we married in August. I am an attending physician in sports medicine and rehabilitation medicine at Changi General Hospital in Singapore.

2009 5th REUNION

Carolina Solis
I was awarded a 2012-2013 Fulbright U.S. Student Program scholarship to study access to emergency surgery in Nicaragua, where I am still working. I'm doing my general surgery training at Duke University Medical Center and will return to Durham this summer to complete my training.

Share Your News

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OBITUARIES

REMEMBERING DISTINGUISHED LIVES

1940s

1942

Ralph M. Fox
April 12, 2013

Herbert R. Morgan
April 24, 2013

Donald C. Nabseth
March 13, 2013

1943

John Moreton
May 27, 2013

1946

Norval E. Christy
May 1, 2013

Kenneth O. Ghormley
March 29, 2013

1947

Charles H. Peete, Jr.
May 26, 2013

1949

Thomas G. Parker
April 7, 2013

1950s

1950

W. Bradford Patterson
April 10, 2013

1952

Merrill I. Feldman
April 27, 2013

1953

Edward L. Ferguson
April 7, 2013

1960s

1960

Joseph R. Barrie
April 8, 2013

1962

Burton E. Sobel
May 3, 2013

1964

Frederick L. Mazer
April 1, 2013

1970s

1972

Stanley I. Hegg
March 21, 2013

1977

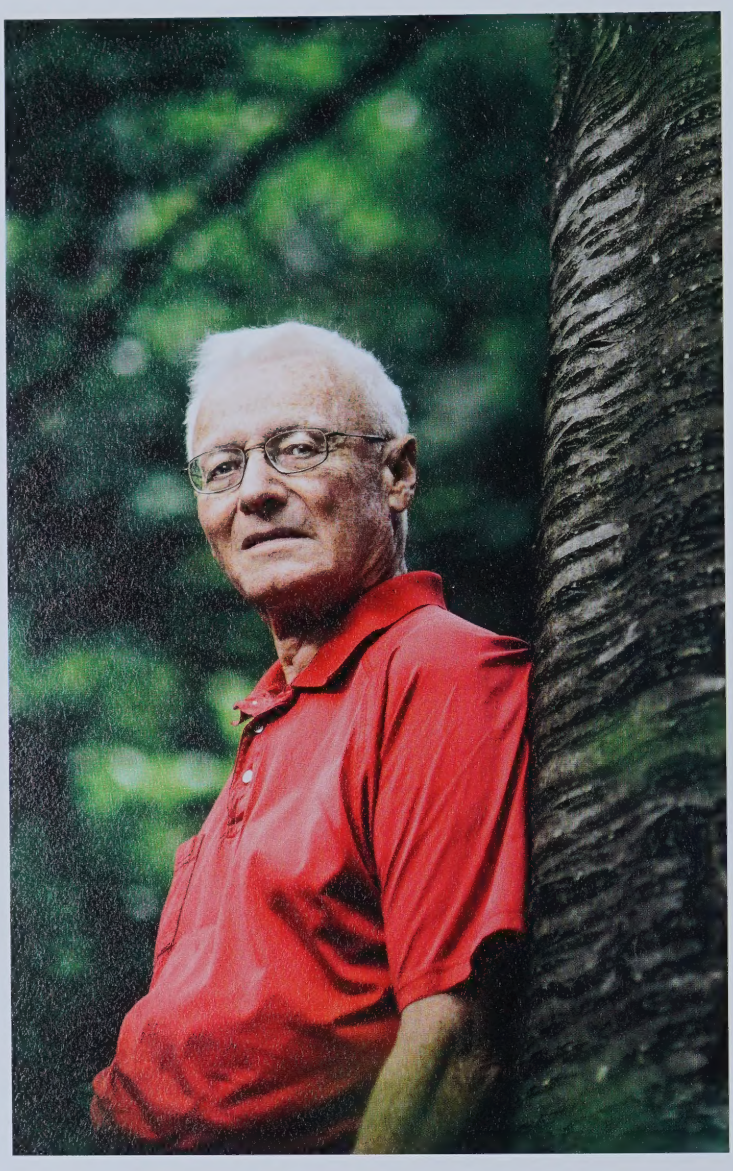
Edison S. Conner
June 1, 2013

This listing of deceased alumni and their dates of death include those alumni whose notices of death were received between March 4, 2013, and June 7, 2013. Links to full obituaries of these alumni can be found at http://alumni.hms.harvard.edu/community/in-memoriam.html.

If you know of an HMS alumna/us who has died recently, please send an email with the link to the obituary to hmsalum@hms.harvard.edu.

TAKING A HISTORY

PROFILE OF NEAL NATHANSON



CLAIMS TO FAME: Associate Dean for Global Health Programs, University of Pennsylvania School of Medicine; former Vice Provost for Research, University of Pennsylvania; former director, Office of AIDS Research, National Institutes of Health; author, *Viral Pathogenesis and Immunity*.

ROLL CALL: "In the middle of my second year of residency, I got hit by the Cambridge draft board," says Neal Nathanson, '53. He was halfway across the country, at the University of Chicago, but as a Cambridge native, he fell under the board's jurisdiction. Called as part of the "doctor draft," Nathanson was to be inducted as a private; he had 30 days to find another commission. "I was desperate," he says. He turned to his chief resident, Tom Grayston, who had just returned to Chicago from two years of draft obligation service in the Epidemic Intelligence Service at the Communicable Disease Center, forerunner to today's Centers for Disease Control and Prevention. "Tom made a call," he says. "Another CDC recruit hadn't shown up, so they agreed to take me on."

ACCIDENTIAL EPIDEMIOLOGIST: On April 12, 1955, a month after Nathanson had joined the EIS, the Francis field trial of the inactivated poliomyelitis vaccine reported successful results. Approval and distribution of the vaccine was immediate. Within two weeks, however, reports of vaccinated children developing paralytic polio drifted in. "This caused a tremendous brouhaha," says Nathanson. Alexander Langmuir, the EIS founder, wasted no time; he created a poliomyelitis surveillance unit, and named the newcomer Nathanson as its chief. "I had no background in epidemiology and no qualifications whatsoever," says Nathanson. With Langmuir's supervision, Nathanson headed a team that traced most of the cases to one manufacturer. The U.S. Department of Health, Education, and Welfare shut that lab down and let the other manufacturers resume distribution.

IN WITH THE NEW: Although encouraged to stay at EIS, Nathanson became fascinated by the basic science of the poliovirus after listening to a talk by David Bodian, a professor at the Johns Hopkins University School of Public Health. "I wrote him informally asking if I could do a postdoctoral fellowship in viral pathogenesis," he says. Once again, Nathanson was lucky. The National Foundation for Infantile Paralysis gave Bodian funds for an additional fellowship.

Nathanson remained at Hopkins for 22 years, but, by the late 70s, research priorities changed and he needed a new home for his basic science research. In 1979, he moved to the University of Pennsylvania's School of Medicine, to become chair of microbiology.

RETURN TO SERVICE: Nathanson's interest in viruses had always focused on those that affect the nervous system. In the 1990s, he began investigating neuroAIDS, also called HIV encephalopathy. He began a research program on the condition, joined the "Baltimore Committee," which was advising the NIH on its developing HIV vaccine program, and ended up as the director of the Office of AIDS Research. In those early days, Nathanson says, life expectancy for those infected was perhaps five years. Then basic science research began to pay off. Drugs could control the virus and make the infection manageable. Today, the life expectancy of an infected 20-year-old—with proper treatment—is 50 years.

—Elizabeth Dougherty

JEFF WOJTASZEK

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Harvard Medical School investigators Galit Lahav, PhD, and Peter Sorger, PhD, are part of an interdisciplinary team working tirelessly to uncover the origins of cancer and develop effective new treatment strategies.

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